MACLEOD'S
PHYSIOLOGY IN MODERN MEDICINE

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PREFACE TO THE NINTH EDITION

In its eighth edition this book was largely rewritten by a group of authors each of whom contributed a section devoted to one of the major fields of physiology. In the present edition that arrangement has been continued. The general plan and purposes of the book, as set forth in the preface to the eighth edition, remain unaltered. It is a pleasure to announce that the same contributors have cooperated in bringing out a ninth edition. They have been joined by Howard J. Curtis who has rewritten the chapters on electrical excitation and conduction of the nerve impulse. Walter S. Root has contributed a chapter on the urinary bladder.

The requirements of students and advances in our knowledge have determined the degree of revision to which each part has been subjected. Experience with the eighth edition has of course suggested a number of changes. Certain parts have been reorganized and many chapters have been completely rewritten. A few subjects which received inadequate treatment in the last edition have been expanded. Although several new chapters have been added, others have been combined; the total number has not been increased.

The bibliography of each of the major sections of the book has again been placed at the end of the volume, and an attempt has been made to render these lists more serviceable by indicating at the top of each page of the bibliography the portion of the text covered. The index has been enlarged with the view in mind that its perusal may afford the student a means of testing his knowledge of the subdivisions and interrelationships of the topics discussed in the text. For assistance in its preparation I am greatly indebted to Mr. Dean K. Crystal and to Mrs. R. B. Bromiley. I especially wish to record my gratitude to Miss Marguerite Stadelhofer, of The C. V. Mosby Company, for many helpful suggestions and for invaluable assistance in bringing the book to press. Again our thanks are due the authors and publishers who have given permission to reproduce many new figures, the sources of which are acknowledged in the legends.

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PREFACE TO THE EIGHTH EDITION

The seventh edition of this book appeared only a short while before the untimely death of Professor Macleod. Since then there has elapsed one of those brief periods which apparently suffice to antiquate any textbook of physiology. It has seemed desirable to bring out a new edition without further delay. When the management of the project became the lot of the present editor, he determined to follow a practice which Professor Macleod had adopted to a greater and greater extent in the successive editions of his book. Accordingly a number of investigators were invited to take part in the enterprise, and the present volume is composed of the contributions of nine individuals. Little of the seventh edition remains. The greater part of the book has been entirely rewritten. Each major subdivision is the work of a writer who is actively engaged in the study of some phase of the subject he treats. The editor is convinced that this is an arrangement which has much to recommend it. The ever increasing bulk of original literature in physiology has made it most difficult for one, or even two or three, individuals to present in adequate fashion the facts and conceptions which should be made available to students and practitioners of medicine. Further, the treatment of each subject by one who has personally launched an experimental attack in some sector of that general field is likely to result in the placing of stress on actual experimental evidence. While it is also likely to inject between the covers some excess of detail, this need not be considered an unmitigated fault. In fact it has the very great advantage that it may stimulate the reader to engage in the weighing of evidence, to achieve an understanding by the selection and coordination of significant facts, in short, to do precisely what every student and practicing physician must do if he hopes to become even mildly competent in his chosen profession.

Prefaces of the earlier editions show that the original purpose of this book was "to serve as a guide to the clinical application of physiology and biochemistry." The first edition consisted largely of a review of those portions of these subjects "which experience has shown to be of especial value to the clinical investigator." Later, as Professor Macleod stated in the preface to the fifth edition, the book was extended "in order that it may also be used as a textbook of physiology for students of medicine," and finally care was taken "to bring up to date those parts of the subject for which no application may be evident." It is hoped that this trend has been continued in the new edition. In the interest of candor it should be stated that the present volume makes no pretense of being a textbook of "applied" physiology. Although it devotes as much attention to clinical data as any of its immediate predecessors, the contributors have in general invoked clinical material only when it illustrates particularly well fundamental physiological principles. Many of the notable contributions of the clinic to the development of physiology have of course been included. The editor trusts that this book will not supply predigested knowledge suitable for immediate bedside application. Nevertheless, the title "Physiology in Modern Medicine" has

been retained. The propriety of this lies in the assumption that the greatest service which physiology can render modern medicine is to continue to solve fundamental problems which are not necessarily of immediate practical concern, to acquaint the student in his preclinical days with the real importance of these and to imbue him with some appreciation of the nature of valid experimental evidence. The point of view is that so admirably expressed by Claude Bernard when he declared: "the prudent and reasonable course at the present moment is to explain all that part of disease which can be explained by physiology, and to leave that which we cannot so explain to be explained by the future progress of biologic science. This kind of successive analysis, which, in its application to pathological phenomena, is carried only so far as the progress of physiological science permits, isolates little by little, by way of elimination as it were, the essential element of the disease which is thus being studied, lays hold of its characters with greater exactitude, and allows therapeutic efforts to be directed with greater certainty. Besides, with progressive analytic advance, the proper character and physiognomy of the disease are preserved. But if, instead of this, some delusive approach of physiology and pathology gives rise to the ambition to explain prematurely at one step the whole of the disease, then one loses sight of the patient, one gets the wrong idea of the disease, and by a false application of physiology, experimental medicine is hindered instead of being assisted in its progress."*

The word "biochemistry" was removed from the title in the seventh edition "because the subject to which it is applied has expanded greatly and has now become a science ancillary to, rather than a part of, physiology in its application to medicine." As the natural and wholly reasonable result of Professor Macleod's own special interests that edition still contained much material which lies within the province of biochemistry. The amount has been somewhat reduced in the new edition. Presentation of biochemical material has been almost entirely limited to those phases of the subject which are essential for the proper elucidation of animal function. The section on "The Physicochemical Basis of Physiological Processes" has not been continued. It dealt with the laws of solution, osmosis, ionization, mass action, the determination of hydrogen ions, colloids, and enzyme action. Most of these are matters with which the student should be familiar before beginning the study of physiology; many receive a good deal of attention in courses and textbooks of biochemistry. Accordingly, it has seemed justifiable to omit those chapters and to utilize the space thus freed for the expansion of other material.

The reader of this book will doubtless be impressed by the variety of experimental methods used by investigators in the field of physiology. Many of the most significant advances have been due to the readiness with which the physiologist borrows from other sciences (and from such arts as surgery) any method which promises to be of assistance in the solution of his problem. The choice of weapons is free. It is to be hoped that restrictions will not be introduced. One should point out, however, that as physiology has grown and recruited more and more followers there has developed a definite

*This passage is from Bernard's "Introduction to the Study of Experimental Medicine," and is the translation of Sir Michael Foster (see page 189 of Foster's "Claude Bernard," London, 1899, T. Fisher Unwin.)

tendency to subdivide the subject on the basis of the techniques used. Too often is "general physiology" defined as the application of the methods of physical chemistry to the study of living things. This perversion becomes all the more curious when one recalls that Claude Bernard, the real author of the term, introduced it to designate that branch of biological science which studies the phenomena common to animals and plants.* Quite recently there has been a tendency to use the term "biophysics" to describe the analysis of biological processes by the methods of physics, a procedure which is by no means new. In so far as this stressing of the application of the methods of chemistry and physics promotes and encourages the acquisition of more exact data, it should be welcomed. But the classification of scientific enquiry by reference to the methods used is a fundamentally unsound procedure which is likely to retard progress. Every worker must of necessity develop special methods of study and in so doing he becomes bound, to a greater or lesser extent, by his technique. The accentuation of this human limitation by the creation of classes of investigators who by restricted training and special title are committed to the application of a species of method is certainly to be deplored. It is only too likely to lead to experimental attacks in which the objective is determined by the applicability of some adroit tactical device rather than by the broader considerations of scientific strategy. This is a question which the student entering on a medical career may ponder with some profit to himself. At any rate let him understand that science is not to be divided by partitions between pieces of apparatus.

The references which appear at the end of this volume may seem unduly extensive. It is not easy to decide, in the case of a book of this sort, how far to go in listing original sources of information. But an arbitrary restriction is bound to give a false impression of the basis of our knowledge, and it has seemed better to err in the other direction, especially when the attempt is being made to present physiology in terms of experimental evidence. Each collaborator fully recognizes that his group of titles omits some important contributions, yet the reader will find in the publications listed a large part of the work on which each section is founded. They should serve as a good basis for any excursion into the original literature.

A word of explanation concerning the use of small type in the text is in order. In general, it can be said that four kinds of material have been presented in this fashion. They are: descriptions of methods; data judged to be of secondary importance to the student, but necessary for a full understanding of the subject under discussion; treatment of matters which are at present largely controversial; and finally considerations which are chiefly of clinical interest. In many places the student will find it helpful to postpone the examination of this material until a second reading.

To the contributors who have helped fill the pages of this book I owe many thanks for the willingness with which they undertook a most laborious task and for their hearty cooperation throughout the joint enterprise. Many individuals have assisted and advised us in our work. It is impossible to name all who have helped the several authors, but let them know that grate-

*In this connection it is interesting to note that in the preface of his unique "Principles of General Physiology" Sir William Bayliss stated that "general" physiology corresponds very closely with what his teacher, Burdon-Sanderson, called "elementary" physiology or "the study of the endowments of living material."

ful acknowledgment of their service is made. In the revision of the chapters on the neuromuscular and central nervous systems I received good advice and much help from my colleagues, Drs. Chandler M. Brooks, Wade H. Marshall, and Clinton N. Woolsey. Dr. Marshall has contributed two cathode ray oscillograph records which he made especially for the book. I wish also to record my gratitude to Mr. and Mrs. R. B. Bromiley and to Miss Grace Grimmel for valuable assistance in the editorial work. Finally, many authors and publishers have cooperated by granting permission to reproduce a large number of new figures, the sources of which are acknowledged in the legends.

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PREFACE TO SEVENTH EDITION

The original purpose of this book—to serve as a guide to the clinical application of physiology and biochemistry—has been kept in view in the present edition and, at the same time, care has been taken to bring up to date those parts of the subject for which no such application may be evident. It is hoped, therefore, that the book will continue to prove useful both to undergraduate students and to practitioners in medicine and surgery. The word "biochemistry" has been removed from the title because the subject to which it is applied has expanded greatly and has now become a science ancillary to, rather than a part of, physiology in its application to medicine. Biochemistry is retained only so far as it is necessary to the elucidation of the problems of animal function.

Many of the chapters have been rewritten so that recent advances in knowledge might be incorporated without disturbing the general continuity or making the volume inconveniently bulky. Another change which it is hoped will be an improvement, is that there is now one bibliography, which has been carefully revised, at the end of the volume instead of separate references at the end of each section. Monographs and original papers are listed separately, and the latter are referred to in the text by numbers. Titles are given in full so that the reader may be informed of the exact nature of the problem dealt with, and the papers selected have, as a rule, been those which seemed to provide the best guidance to the complete literature of the subject.

The section on the neuromuscular and the central nervous systems, contributed in several previous editions by A. C. Redfield, has been taken over by Philip Bard, and has been largely rewritten on account of the changed interpretations that the recent advances in these subjects have brought about. Other new contributors in the present edition are J. M. Peterson, who has revised the introductory chapters, and E. P. Carter, who has revised the section on circulation. I am deeply indebted to these as well as to my other collaborators. I wish also to record my thanks to H. R. Noltie for his painstaking work in checking the references and in revising the index.

I have also to thank The Oxford University Press, H. M. Controller of Documents, London, and other authors and publishers, for permission to reproduce certain figures, the sources of which are acknowledged in the legends.

J. J. R. Macleod.

Aberdeen, Scotland,
1935.

PREFACE TO FIRST EDITION

The necessity of allotting the various subjects of the medical curriculum to different periods, so that the more strictly scientific subjects are completed in the earlier years, has the great disadvantage that the student, being no longer in touch with laboratory work, fails to employ the scientific knowledge with full advantage in the solution of his clinical problems. He is apt to regard the first two or three years in the laboratory departments as inconsequential in comparison with the supposedly more practical instruction offered during the subsequent clinical years. He is taught by his laboratory instructors to observe accurately, and to correlate the observed facts, so that he may be enabled to draw conclusions as to the manner of working of the various functions of the animal body in health, and before proceeding to his clinical studies, he is required to show a proficiency in scientific knowledge, because it is recognized that this must serve as the basis upon which his knowledge of disease is to be built. When the clinic is reached, however, the methods of the scientist are not infrequently cast aside and an understanding of disease is sought for largely by the empirical method; namely, by the endeavor to see and examine innumerable patients, to diagnose the case according to the grouping of the signs and symptoms, and to treat it by the prescribed methods of experience. So much has to be learned and so much has to be seen during the clinical years, that the student gives little thought to the nature of the functional disturbance which is responsible for the symptoms; he fails to realize that, after all, there is no essential difference between the condition brought about in his patient by some pathological lesion, and that which may be produced in the laboratory by experimental procedures, by drugs or by toxins. It must of course be recognized that just as the science of medicine originated by the grouping of symptoms into more or less characteristic diseases for which the most favorable method of treatment had to be discovered by experience, so must a certain part of the medical training be more or less empirical but it should at the same time be realized that such a method is only a means to an end, and that the real understanding of disease can be acquired only when every abnormal condition is interpreted as a primary or secondary consequence of some perverted bodily function, and when the training in observation and the inductive method is carried from the laboratory into the clinic.

It is a constant experience of clinical instructors who would employ scientific methods of instruction, that they find the students not only indifferent to an analysis of their cases from the functional standpoint, but also that they are too inadequately prepared in fundamental physiological knowledge, to make the analysis possible. The student may have a superficial acquaintance with the main facts of physiological science but have failed to acquire the enquiring habit of mind which will enable him, through reflection, comparison, and personal research, to apply the knowledge in practical medicine and surgery.

For this lack of correlation between the laboratory and clinical studies, the clinical instructors are not alone responsible. The laboratory courses are

frequently given without any attempt being made to show the student the bearing of the subject in the interpretation of disease, or to train him so that in his later years he may be able to adapt the methods of investigation which he learned in the laboratory, to the study of morbid conditions. It is self-evident that (without any knowledge of disease) the extent to which the student in the earlier years of the course could be expected to appreciate the clinical significance of what he learns in the laboratory is limited, but this should not deter the instructor from indicating whenever he can, the general application of scientific knowledge in the interpretation of diseased conditions. But the chief remedy of the evil undoubtedly lies partly in the continuance of certain of the laboratory courses into the clinical years, and partly in the study of medical literature in which the application of physiology and biochemistry in the practice of medicine is emphasized.

Notwithstanding the sufficient number of excellent textbooks in physiology available to the medical student, there is none in which particular emphasis is laid upon the application of the subject in the routine practice of medicine. In the present volume the attempt is made to meet such a want, by reviewing those portions of physiology and biochemistry which experience has shown to be of especial value to the clinical investigator. The work is not intended to be a substitute, either for the regular textbooks in physiology, or for those in functional pathology. It is supplementary to such volumes. It does not start like the modern text in functional pathology, with a consideration of the diseased condition, and then proceed to analyze the possible causes and consequences of the disturbances of function which this exhibits; but it deals with the present-day knowledge of human physiology in so far as this can be used in a general way to advance the understanding of disease. In a sense it is therefore an advanced text in physiology for those about to enter upon their clinical instruction, and at the same time, a review for those of a maturer clinical experience who may desire to seek the physiological interpretation of diseased conditions.

In attempting to fulfil these requirements, it has been deemed essential to go back to the fundamentals of the subject, and to explain as simply as possible the physical and physicochemical principles upon which so large a part of physiological knowledge depends. Physiology may be considered as an application of the known laws and facts of physics and chemistry to explain the functions of living matter, and it is only after the extent to which this application can be made has been appreciated, that the knowledge may be used to serve as the foundation upon which a superstructure of clinical knowledge can be built.

In order that the volume might be maintained of reasonable size, it has been necessary to select certain parts of the subject for particular emphasis, the basis of selection being the degree to which our knowledge clearly shows the value of the application of physiological methods both of observation and of thought in the study of diseased conditions. This has not been done to the extent of omitting the apparently less essential parts, for these have been treated in sufficient detail to link the others together so as to preserve a logical continuity, and show the bearing of one field of knowledge on another. There are, however, certain parts of the science, particularly the physiology of nerve and muscle, of the special senses, and of reproduction, for which

application in the general fields of medicine and surgery is limited, and these parts have been omitted entirely. It has been judged that this perhaps somewhat arbitrary selection is justified on the ground that the ordinary text in physiology covers these subjects sufficiently, except for the specialist, for whom, on the other hand, no adequate review would have been possible within the limits of such a volume as this. With reference to biochemistry, no attempt is made to review the properties or describe the characteristic tests of the various chemical ingredients of the body tissues and fluids. This is already sufficiently done in the textbooks on biochemistry, and in the numerous manuals on clinical methods. Biochemical knowledge is treated rather from the physiologist's standpoint, as an integral part of his subject, particular attention, nevertheless, being paid to the far-reaching applications of this latest department of medical science, in the elucidation of many obscure problems of clinical medicine, such as those of diabetes, nephritis, acidosis, goiter and myxedema. To make the volume of value to those who may not have had time or opportunity to familiarize themselves with the technical methods of the physiologist and biochemist as used in the modern clinic, a certain amount of space is devoted to a brief description of the methods that appear at present to be receiving most attention, and to be of greatest value.

Finally, it should be mentioned that the principles of serum diagnosis and therapy are omitted, since these belong to a highly specialized science requiring an intensive training of their own.

In the hope that the volume may be instrumental in arousing sufficient interest to stimulate a more intensive study of the various subjects which it introduces, a brief bibliography is given at the end of each section. The references selected are to papers that are more particularly known to the author; they are not necessarily the most important publications on the subject, but are often chosen because of the useful reviews of previous work contained in them, rather than because of their own originality. Some of the papers, however, are referred to as authority for statements of fact which may arouse in the reader a desire to ponder for himself the evidence upon which these are based. The references are usually divided into two groups, "monographs" and "original papers," and it is only occasionally that specific reference is made to the former in the context. The original papers, on the other hand, are referred to by numbers. With the general field of the subject so well covered by such excellent textbooks as Bayliss' "Principles of General Physiology," Stewart's, Howell's, Starling's, and Halliburton's "Human Physiologies," and Leonard Hill's "Recent and Further Advances in Physiology," the author has felt free to pick and choose, from the monographs and original papers, topics that are ordinarily passed over cursorily in the textbook, and when this has been done, the references are somewhat more extensive. Such is the case for example in the chapters relating to the chemistry of respiration, to the metabolism of carbohydrates and fats, to the problems of dietetics and growth, to the physicochemical basis of neutrality regulation in the animal body, and to the action of enzymes.

Acknowledgment is gratefully made for the assistance and advice in the preparation of the book, particularly to R. G. Pearce, for the contribution of several chapters, to which his name is attached, and for which he is entirely responsible; and to E. P. Carter, whose criticisms, after patient perusal of the

unfinished manuscript, were of inestimable value in its final revision. Acknowledgement is also made to R. W. Scott and F. E. Lloyd, for valuable criticism and advice, and to the former for a chapter on the "Clinical Application of Electrocardiographs." To Miss Achsa Parker, M.A., the author owes a great debt of gratitude for the thorough and painstaking way in which she prepared the manuscript for the press, and for her never-tiring endeavors to have the spelling and punctuation in conformity with Webster's Dictionary. For assistance in the preparation of the index thanks are due to Miss Marion Armour and Mrs. MacFarlane, and for permission to use certain of the figures and illustrations, to the various authors and publishers who granted it. For the excellent management and careful execution of the presswork, the author wishes to thank the publishers, whose courteous and friendly dealings have always made the work easier.

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By Philip Bard

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PART I

THE NEUROMUSCULAR AND CENTRAL NERVOUS SYSTEMS

By Philip Bard*

CHAPTER I

THE EVOLUTION OF THE NEUROMUSCULAR MECHANISM

Disease of the nervous system confronts the physician with a complex group of symptoms, a syndrome due to more or less sharply localized disturbances in its function. It is the province of physiology to analyze the fundamental activities of the nervous system and assign to various parts a functional significance, so that the complicated picture presented by disease may be recognized as the logical result of a lesion of definite nature, location, and extent. We find the symptoms of nervous disease grouping themselves as disturbances (1) of sensation (anesthesia, etc.); (2) of movement, both volitional and reflex (paralysis, etc.); (3) of postural coordination (muscular spasms, flaccidity, ataxia, etc.); (4) of the mechanisms of integration in the nervous system including the higher mental functions of association, memory, and attention.

Corresponding to each of these groups we can recognize a definite aspect of nervous activity, the successful performance of which depends on the continuity of more or less precisely known groups of cells within the nervous system, and disturbances of any of these aspects can be assigned to lesions affecting some part of the group of nerve cells on which they depend.

The fundamental function of the nervous system is to correlate the activities of the body so that its many parts may act harmoniously and as a unit in preserving the welfare of the individual. What the basis of this integration of activity which manifests itself so remarkably in the behavior of the higher animals is, can best be illustrated by a consideration of its evolutionary development.

PRIMITIVE NEUROMUSCULAR MECHANISMS

In the unicellular organisms three processes occur when a response is brought about by a stimulus. These are (1) *excitation*, or the setting up of a physiological disturbance; (2) *conduction*, or the spread of the disturbance to parts of the

*Chapters II and VII of this Part have been written by Howard J. Curtis.

cell remote from the point of excitation; and (3) *response* on the part of the protoplasm to which the disturbance has spread. Thus when a *paramecium* swims against a hard object, an excitation is set up by the contact at its anterior end; the disturbance so produced spreads to other parts of the cell and causes the reversal of the direction of the stroke of the cilia in relatively remote regions, with the result that the *paramecium* backs away from the obstacle, and then starts off in another direction. The three fundamental processes of excitation, conduction, and response occur whenever the neuromuscular system of an animal is brought into play. The case of multicellular animals differs from that cited above only in that the conduction is *intercellular*, so that the disturbance set up by an excitation spreads from one cell to another.

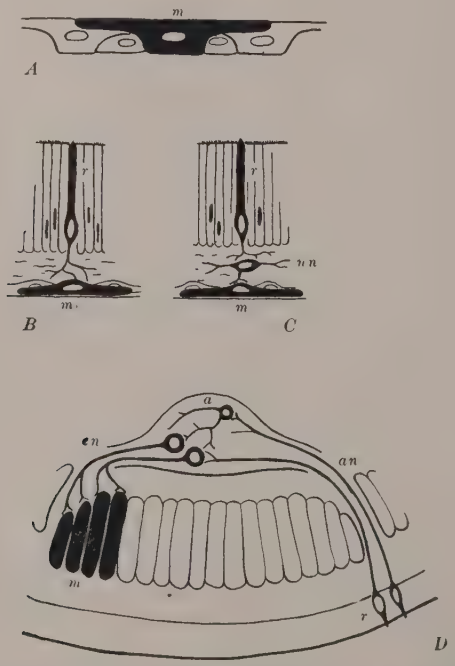

Fig. 1.—The evolution of the nervous system. *A*, the independent effector as illustrated by the muscle cells of the sponge; *B*, a receptor-effector system such as occurs in the tentacles of sea anemones; *C*, the neuromuscular mechanism of the trunk of the sea anemone, in which a network of nerve cells is interposed between receptor and effector; *D*, the nervous system of the earthworm, illustrating a typical reflex arc and the occurrence of association neurons; *a*, within the ganglion; *r*, receptor; *nn*, nerve net; *an*, afferent neuron; *en*, efferent neuron. (Modified after Parker, Prentiss and Bayliss.)

There exist in multicellular animals many examples of cells independent of the influence of nervous tissue which respond directly to stimuli. These are known as *independent effectors*. The most primitive muscle cells known are those which close the terminal pores of sponges, thus regulating the flow of water through these animals. Parker[2] has shown that these muscles respond to a variety of stimuli in spite of the fact that no nerve cells can be found in association with them. Ciliated epithelial cells, such as occur in certain ducts and

passageways in man, are also independent effectors, acting independently of nervous control. The ameboid white blood corpuscles also must be quite comparable in their mechanisms of response to the protozoa.

The forerunner of nervous conduction is seen in the activities of these independent effectors. If a field of ciliated epithelium is examined microscopically, it is found that the cilia are not beating in a disorderly way, but that definite waves are passing across the field, each cilium beating a moment later than the preceding one. The appearance is quite like that produced by gusts of wind sweeping across a field of grain. In the sponges, also, a stimulus applied several centimeters from the terminal pore will cause its muscles to contract in spite of the absence of nervous tissue connecting the muscles with the point of stimulation. This type of intercellular conduction by nonnervous tissue is called *neuroid transmission.* It illustrates the significant fact that conductivity is not a specific property of nervous tissue, but is displayed by many other tissues as well.

Nervous tissue makes its first appearance in the *coelenterates* (Fig. 1). A most primitive condition is found in the tentacles which surround the mouth of the sea anemone. At the base of certain epithelial cells fibrous processes are developed which connect with underlying muscles. The epithelial cell serves as a receptor for stimuli, and transmits the disturbances set up by them to the muscle or effector. Such a mechanism is called a *receptor-effector system.* The responses which it brings about are purely local, since there is no provision for conducting the disturbance to remote parts of the animal, but the introduction of the receptor serves a valuable purpose in increasing the sensitivity of the system. Moreover, the arrangement is adequate for the purpose for which it is employed, which is to cause the tentacle to bend toward a particle of food situated between it and the mouth, so that the currents set up by the cilia with which the tentacle is covered may sweep the food into the mouth. An arrangement quite similar to the receptor-effector system of the *coelenterates* is found in the axon reflexes of mammals, in which disturbances set up in certain sensory neurons spread directly through collateral fibers to the muscles of the cutaneous blood vessels (page 177).

THE NERVE NET

In the trunk of the sea anemone nervous tissue assumes a much more important rôle. Between the receptors of the epithelium and the muscles there is interposed a layer of nerve cells arranged as a network. This network can transmit disturbances set up in the receptors to quite distant muscles, with the result that a local stimulus may bring about a generalized contraction of the trunk. The primitive nervous system is thus seen to consist of a network of nerve cells or *nerve net.* The structure of this system is such that nerve impulses set up in one region can spread at random to all parts of the nerve net. The responses produced by such a mechanism are necessarily diffuse in character, since large groups of muscles will be brought into play at one time. Since conduction is not limited to definite paths in the nerve net local injury will have little effect on the reactions of the organism because the nerve impulses can pass around the injured region through other parts of the nervous network. The rapidity with which impulses are conducted by the nerve net is not great, being of the order of 130 millimeters a second, or about two hundred times less than the velocity of the nerve impulse in the motor nerves of the frog.

On the basis of the work of Bethe and others it has been thought that the individual cells of the nerve nets of coelenterates are linked together in protoplasmic continuity so that the structure is essentially a syncytium. On this assumption Parker gave to the cellular unit of the nerve net the name *protoneuron*, to distinguish it from the unit of the central nervous systems of higher forms which has long been called a *neuron* and which the majority of anatomists regard as a structure whose substance does not fuse with that of other units. The more recent work of Bozler,[1] however, confirms the earlier observation of Schäfer that the relation between the filaments of the nerve net is one of contiguity; cell membranes are interposed between the nerve filaments so that transmission must occur across a cell junction. Consequently the structure is not a true network. From an anatomical point of view this means that no sharp distinction can be drawn between protoneurons and neurons. Furthermore, if the histological separation of the cells of the nerve net by membranes be correlated with a polarity of conduction across them, we have in the diffuse primitive nervous system one fundamental feature of the central nervous systems of higher forms, namely, the synapse. However this may be, the connections between individual cells of the nerve net are so numerous that conduction, athough unidirectional at any one synapse, is bound to be diffuse.

In most of the invertebrates which possess a central nervous system a peripheral netlike arrangement similar to that of the coelenterates is present. It has even been claimed that the nerve net is retained in many parts of the higher animals. The mammalian myenteric plexus is regarded by some as nothing more than a syncytial nerve net of a most primitive type, but competent neuro-anatomists are unable to agree with this interpretation. It is now certain that many of the cells found in the myenteric plexus represent the postganglionic neurons of the parasympathetic innervation of the gastro-intestinal tract. For example, it has been shown that during embryonic development the cells which form the enteric neurons of the mammalian stomach migrate out from the region of the hind-brain and thus do not have a peripheral origin characteristic of the elements of the nerve nets of invertebrates.

THE CENTRAL NERVOUS SYSTEM

The outstanding characteristic of the elementary nervous system is its arrangement for conducting nerve impulses diffusely in all directions throughout the body. The central nervous system of higher forms has evidently developed from the diffuse type of system, and it is characterized by the property of selectively discharging impulses from diverse receptors to effectors so as to bring about a degree of coordination between parts that is beyond the capacity of the more simple arrangement. The central organ is like the diffuse system in arising in the region between receptor and effector, but it is formed focally from the superficial ectoderm by a process of inward migration. Parker has shown how well this process is illustrated in the series of annelids. In *Sigalion* a brain and ventral nerve chain forms a band which is still part of the ectoderm. In *Nereis*, a somewhat higher form, the ventral chain has, by a process of delamination, freed itself from the skin, although the brain is still a part of that layer. In the earthworm the process has gone still further and the entire central nervous system has separated from the ectoderm and lies embedded in the interior of the organism. The development of the vertebrate brain is characterized by a similar inward migration of a portion of the dorsal ectoderm to form a neural tube.

The nerve cells of which any central nervous system is composed are termed *neurons*. Because any given neuron arises from a germinal cell or neuroblast of the ectodermal neural band or plate and maintains its cellular individuality throughout histogenesis, it is a *genetic unit*. When completely developed, it consists typically of a nerve cell body containing the nucleus, from which extend numerous short processes, or *dendrites*, and one long fiber, or *axon*. The axon may branch many times, such branches being called *collaterals*. The majority of anatomists today agree that nerve cells remain anatomically separate, that where

the axon collaterals of one neuron meet the dendrites and cell body of another neuron there is contiguity, not continuity of substance. Thus the neuron is an *anatomical unit*. In support of this concept is the indubitable fact that the neuron is also a *trophic unit*. Any part of a nerve cell which is severed from its

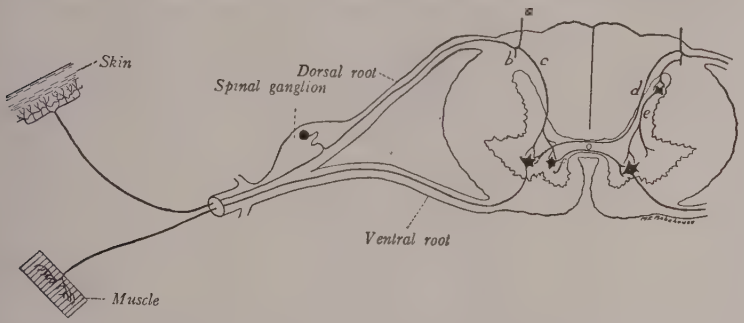

Fig. 2.—A diagrammatic representation of a section through a mammalian spinal cord and a spinal nerve to illustrate a simple spinal reflex arc: *a*, *b*, *c*, and *d*, are branches of sensory fibers of the dorsal roots; *e*, an internuncial neuron; *f*, a commissural neuron. (From Ranson: *The Anatomy of the Nervous System*. W. B. Saunders Co.)

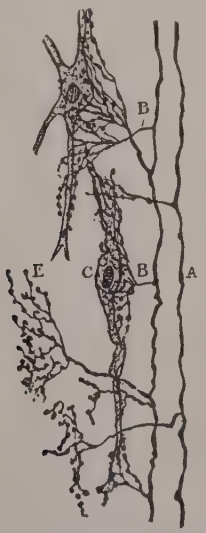

Fig. 3.—Arborization of collaterals from the dorsal root fibers around the cells of the posterior horn. *A*, ascending fiber in dorsal columns; *B*, collaterals; *C*, cells of dorsal horn; *E*, synapses. Note the many end knobs (synaptic knobs) which make the actual contacts between presynaptic fiber and the dendrites and cell body of a central neuron. (From Ramon y Cajal.)

nucleus degenerates, but regeneration of a divided axon may occur by outgrowth from that part still in connection with the cell body. Again, the division of an axon leads to chromatolysis in the cell body. When injury evokes degeneration or chromatolysis, the changes are confined to the injured neuron and do not

Fig. 4.—Diagram of nervous system of segmented invertebrate; *a*, supraesophageal ganglion; *b*, subesophageal ganglion; *oe*, esophagus or gullet.

spread across intercellular boundaries to contiguous neurons.* The neuron is also the *functional unit* of the nervous system; neurons are the only elements concerned in the conduction of nerve impulses.

The points of contact between individual neurons are called *synapses.* Because of various technical difficulties it has been difficult to determine precisely the structural nature of the synapse, but wherever this subject has been investigated, it has been found, with few exceptions, that the junction between any two neurons is formed by multiple points of contact. Thus Cajal found that many axon collaterals terminate as *end knobs* or *boutons terminaux,* swellings which are applied to the surface both of the dendrites and of the cell bodies of other neurons (Fig. 3). Where there are synapses conduction of excitation appears to take on certain characteristics that are not found elsewhere, e.g., in nerve trunks composed of axons. Although this is a subject that must be deferred to a later chapter, one important fact may be mentioned at this point. The inference made by Cajal and van Gehuchten on anatomical grounds that normally conduction is always cellulipetal in dendrites and cellulifugal in axons has the support of many physiological facts. For example it is known that a motor or sensory nerve fiber can conduct in either direction. When, however, the path of conduction involves a synapse the passage is invariably unidirectional; i.e., from axon collateral to dendrite or cell body, never in the opposite direction. The arrangement of neurons in a simple type of central nervous system, such as that of the worms, is characteristic. Most of the nerve cell bodies are collected together in segmentally arranged masses or *ganglia.* Fibers pass from receptors in the epithelium and other parts to the ganglion of the same segment while other fibers originating from nerve cell bodies within the ganglion pass in other trunks to the muscles of the same segment. In addition, fibers pass from one ganglion to the next or to distant ganglia in trunks known as interganglionic connectives.

In order that a muscular response may result from a stimulus applied to the skin of a worm, a disturbance must pass through the following structures: (1) the receptor with its afferent fiber, (2) a motor neuron with its efferent fiber, to (3) the muscle (or other effector). The group of structures is called a *reflex arc.* It is the simplest anatomical arrangement in the central nervous system capable of bringing about a significant motor response. The activity produced by such a mechanism is called a *reflex.*

The reflex arc as we have described it lies frequently within a single segment of the worm. Consequently, it can provide each segment with a great de-

*This statement is generally applicable, but it should be pointed out that instances of antegrade or *transneuronal degeneration* are known. Thus after section of one optic tract the cells of alternate layers of the lateral geniculate body of the same side regularly degenerate within a few weeks. This is an example of a rather rare phenomenon. It is not at all generally true that nerve cells degenerate when their afferent connections are interrupted.

gree of autonomy, so that many of its activities are undisturbed by the removal of other parts of the animal. No provision is made by such an arrangement for correlating the activities of adjacent segments. The ganglia of worms contain an additional type of neuron which makes the correlation of the activities of different segments possible. These are neurons which lie entirely within the central nervous system. Their axons lie in the interganglionic connectives and serve to connect afferent fibers in one segment with motor neurons in some distant segment. They also form alternative pathways between sensory and motor neurons. They are called *association* or *internuncial neurons.*

The fundamental characteristics of the central nervous system as it appears in the worms consist in (1) the individuality of the component nerve cells and their specialization for certain functions, (2) the arrangement of the neurons in such a way that the impulses must pass over definite paths or reflex arcs in order to reach an effector, (3) the introduction of neurons specialized to associate the activities of reflex arcs in remote parts of the body, and (4) the segregation of the greater part of the nervous tissue into a centrally located chain of ganglia, from which fibers pass to peripheral structures in definite nerve trunks. These characteristics persist in the central nervous system in the higher animals, including man.

Certain modifications of the simple arrangement found in the worms have been introduced into the nervous system as the motor activities of organisms became more precise and complex. Of minor importance may be mentioned the introduction of an afferent nerve cell distinct from the receptor between the latter and the central ganglionic mass (see the evolution of receptors, page 65) and the introduction of an outlying neuron between the termination of the primary motor neuron and the visceral effector organ (see the autonomic system, page 165). Of far greater importance is the great increase in the number of internuncial or association neurons which become the salient feature of the vertebrate nervous system. In the worms the interganglionic connectives are scarcely more bulky than the peripheral nerves from a single ganglion, whereas in the central nervous system of man the number of the fibers extending from segment to segment exceeds by many times the number of fibers in any single pair of spinal nerves. This increase in the mass of the central portion of the nervous system is not distributed equally in all parts, but tends to be concentrated particularly at the anterior end. Even in the worms the most anterior ganglion, the supraesophageal ganglion, is larger than the others, while this tendency finds its culmination in the great bulk of the brain in man. This process of *cephalization* is obviously correlated with the development of special sense organs at the anterior end of the animal: the sense of taste at the mouth, the tactile organs found on the tentacles which adorn the head of many invertebrates, and of special receptors for stimuli originating at a distance, such as the eye and ear. The development of association neurons for the correlation of activities initiated by the stimulation of these receptors has made this portion of the central nervous system the natural place for the seat of the higher nervous functions as they evolved.

CHAPTER II

ELECTRICAL EXCITATION AND THE RELATION OF STIMULUS TO RESPONSE

By Howard J. Curtis

We have seen that the activity of the neuromuscular mechanism involves the three processes of excitation, conduction, and response. These processes may all be exhibited by a single cell. The evolution of the neuromuscular system is the history of a gradual specialization of cells each for the execution of one of these processes. Thus in a reflex arc the receptor is a cell primarily fitted to react to slight changes in its environment, the neurons are especially adapted to the conduction of impulses, and the effector is constructed for the sole purpose of carrying out motor responses or producing some specialized secretion. It would appear as though a single cell could not develop the ability to perform all of these functions with perfection, and as a consequence a high degree of division of labor has been established.

It should be remembered, however, that this specialization for one process has deprived the cells to only a limited degree of the ability to be the seat of the other processes. Thus, although excitability is primarily a property of the receptors, nerve cells must also retain the ability to become excited by disturbances set up in the receptors, and muscles must be able to be excited by impulses reaching them from motor neurons. Similarly, conduction must occur not only in nerve cells, but also in receptors, so that a disturbance set up at the distal end of the receptor cell may reach the nerve fibers which terminate about its proximal end. Muscle cells also must be able to conduct disturbances set up in the neuromyal junction to all parts of the muscle fiber, so that they may contribute to the response. It will be seen that conduction of excitation in cardiac muscle is of great importance in the coordination of the action of the heart (Chapter XXX).

While these three fundamental processes are common to all irritable tissues, it is convenient to study each in that tissue in which it is most highly developed and where other processes introduce a minimal complicating element. For this reason, in the chapters which follow, we shall examine conduction in nerve, mechanical response in muscle, and devote some attention to the excitability exhibited by receptors. Since excitation is apparently of the same nature in all three places, it will avoid repetition if we take up its general aspects at this point.

First of all it is necessary to define certain concepts. *Excitability* is the tendency of a cell or tissue to respond to a change in its environment, external or internal. The *stimulus* is any environmental change which causes an *excitatory process* to be set up in the tissue. This process occurs locally at the point of stimulation; since it is apparently identical in all excitable tissues, it may be distinguished from the response. When a stimulus of any one kind is applied

to a tissue it is found that it must have a definite minimal value in order to excite. The *minimal stimulus* is also called a *threshold stimulus,* for it has that value which is just sufficient, as it were, to cross the threshold of excitability. It gives, in fact, a measure of excitability and we may write the equation:

$$\text{Excitability} = \frac{1}{\text{Value of minimal stimulus}} = \frac{1}{\text{Threshold}}$$

As we shall see, the passage of a current of subthreshold value through a tissue exerts important effects on the excitability of that tissue, although it does not excite.

A stimulus of just threshold value produces in cardiac muscle, in single nerve fibers, and in individual skeletal muscle fibers excited through their nerves, a response which is maximal for the tissue under the conditions prevailing at the time. Stimuli of greater than threshold value do not produce a greater response. This fact, that the magnitude of the response is independent of the magnitude of the stimulus, is expressed by saying that the tissue obeys the *all-or-none law.* Since, however, skeletal muscles and nerves are composed of large numbers of functionally independent units, graded stimuli applied to the tissue as a whole may produce graded responses. At a certain value above threshold the stimulus excites all the units, and the greatest possible response results. A stimulus of that size is termed a *maximal stimulus.* Since they produce no greater effect, and are likely to damage the tissue, *supramaximal stimuli* are to be avoided in experimental work. Adequate stimuli of values below maximal are called *submaximal stimuli.*

A number of environmental energy changes are adequate stimuli for most tissue cells. They may be osmotic, chemical, thermal, or mechanical, but in physiological investigations of excitability it is the general rule to employ a brief electric current as stimulus because it can be controlled very accurately as regards strength and duration and because it can be applied repeatedly without producing signs of injury. The electrical form of stimulation is also satisfactory because in all probability the process of excitation itself is electrical. The current used may be either galvanic or faradic. There is no fundamental qualitative difference between these two kinds of currents, but since galvanic stimulation is more readily analyzable than faradic, it has been more generally employed in studies of the excitatory process in nerve and muscle. There have emerged from investigations in this field certain "laws" of excitation. When considered together, they give some indication of the fundamental nature of the excitatory process and for that reason they have great theoretical interest. Knowledge of these facts, however, is of considerable practical importance to any one studying the responses induced by electrical stimuli.

These laws of excitation are qualitatively the same for all excitable tissues, but they are most easily demonstrated with nerve. If two electrodes are placed along the length of a nerve, and are connected to a battery or other suitable source of electromotive force, then an electric current will flow along that portion of the nerve between the two electrodes. Part of the current will flow only through the intercellular fluid bathing the nerve fibers, and part will traverse the cell membranes and flow through the cytoplasm of the cells (Fig. 5). Only that fraction of the current which penetrates the cell is effective in

altering its excitability or in stimulating it. Since different nerve fibers have relatively different amounts of intercellular fluid surrounding them, it is not possible to compare directly the true threshold currents for different nerves. Furthermore, the excitability of the nerve is altered only in those regions where the current is flowing across the cell membranes, i.e., a current which flows only through the cytoplasm of the cell causes no change in excitability. This shows that it is primarily the cell membrane which is concerned with the active process of excitation.

When a current is sent through a nerve the excitability of the nerve changes whether a response is elicited or not, and this change is a function not only of the current strength but of the time after the application of the current.

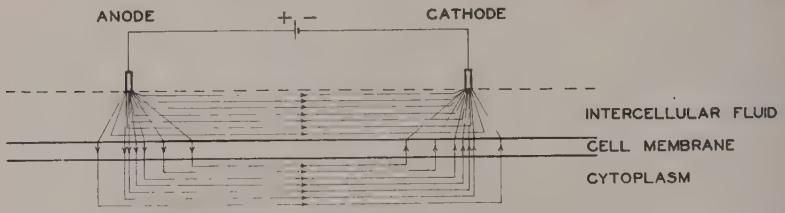

Fig. 5.—Diagram showing the flow of current in and around a single nerve fiber.

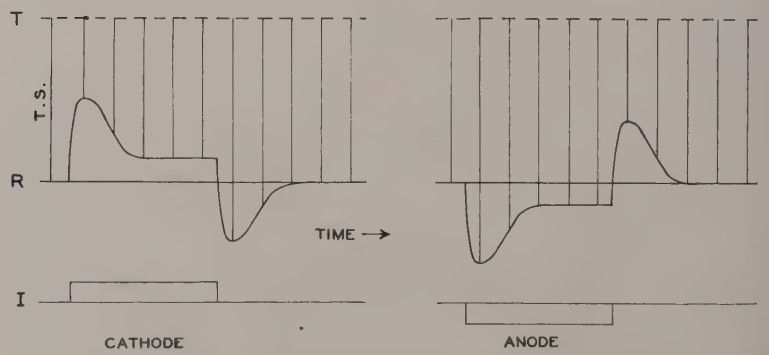

Fig. 6.—Diagram showing the changes in excitability at the cathode and anode due to the passage of a current, *I*. *R* is the resting excitability and *T* the threshold. Excitability is measured by brief test shocks, *T.S.* (Modified from Cole: Cold Spring Harbor Symposia on Quantitative Biology **1**: 131, 1933.)

When the current is turned off, the excitability does not immediately return to its resting value, but exhibits certain fluctuations before doing so. Furthermore, these changes are quite different, depending on whether the current is flowing into (anodal) or out of (cathodal) the nerve cell. The excitability can be measured at any instant by applying a brief electric shock of an intensity just sufficient to cause a response (threshold value). These changes in excitability are represented graphically in Fig. 6. Here a constant current of subthreshold strength, *I*, is sent through the nerve, for a time indicated in the lower part of the figure. The size of brief threshold test shocks is indicated by the lengths of the vertical lines, *T.S.*, which are a measure of the amount of

stimulus which must be added to bring the excitability to threshold. The smooth curve drawn through the lower ends of these lines shows the excitability at every instant. This diagram, first proposed by Cole,[3] represents nearly all the known features of electrical stimulation. It indicates the following facts:

1. An electric current, however weak or brief its duration may be, leaves the nerve in an altered state of excitability for a time after the current has ceased to flow. Thus the summation of two brief subthreshold cathodal shocks may give a response, if the time interval between them is not too great. This is known as the *summation of inadequate stimuli.*

2. During the passage of a constant current the excitability is increased at the cathode and decreased at the anode. These phenomena are sometimes called *catelectrotonus* and *anelectrotonus,* respectively. If the anodal current is made strong enough, excitability may be lowered sufficiently to block the passage of a nerve impulse.

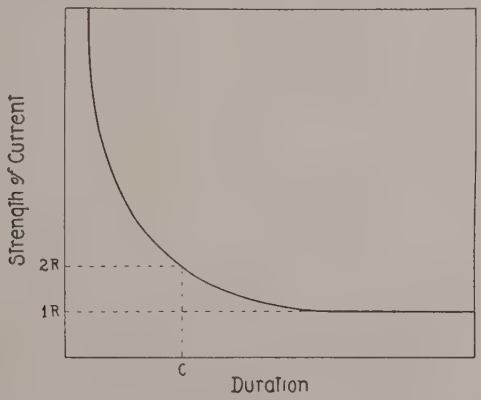

Fig. 7.—Diagrammatic strength-duration curve of electrical excitability. *1R,* rheobase; *C,* chronaxie (Lapicque) or excitation time (Lucas, Rushton). (From Davis and Forbes[4] after Rushton.)

3. If the current, *I,* is made strong enough, then the excitability will rise to a threshold value at the cathode after the make of the current, and if made still stronger will reach threshold at the anode after the break of the current. The threshold strength of a cathodal current of long duration is usually called the *rheobase.*

4. If a response is not elicited within a certain time after the make of the current, the *utilization time,* there will be no response regardless of how long the current is allowed to flow. If the stimulus is supramaximal, obviously the excitability will reach threshold sooner.

5. At the cathode the excitability, after reaching a maximum, tends to return to its resting value. This phenomenon is known as *accommodation.* If the current is increased gradually instead of being applied abruptly, accommodation, which acts relatively slowly, will tend to prevent the attainment of the threshold. Thus slowly rising currents may be passed through the nerve and attain very high values without eliciting a response.

6. If the cathodal current is stopped before the maximum point on the excitability curve is reached, the excitability will not rise as high. In other words, with current pulses of short duration, it is necessary to use a current of greater intensity to reach the threshold; and the shorter the duration, the greater the required intensity. Thus a relation exists between the strength of the threshold current and its duration, and this relation, known as the *strength-duration curve,* is plotted in Fig. 7. Since most electrical stimulation is performed with short current pulses, the strength-duration curve has considerable practical as well as theoretical importance. It shows that for current pulses of extremely short duration, very high current strengths are required to cause

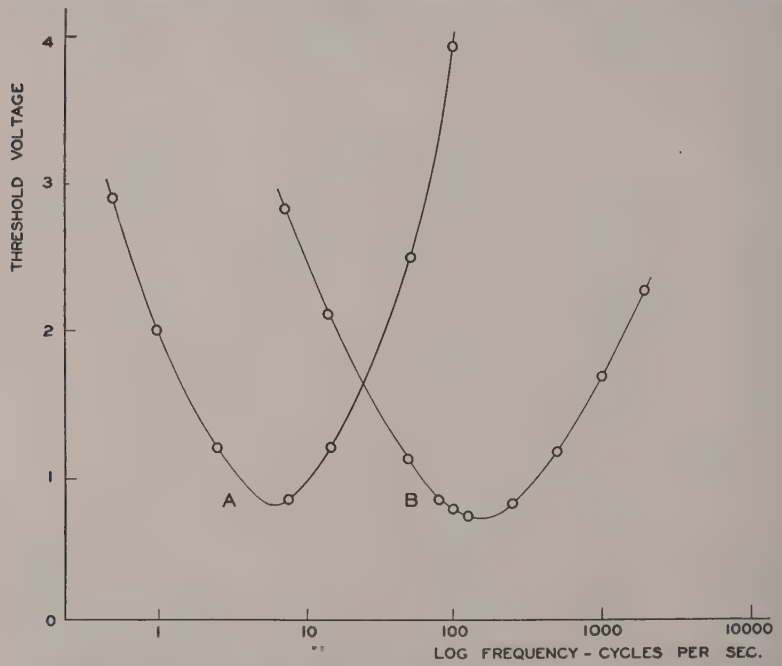

Fig. 8.—Curves showing the relation between the threshold voltage and frequency for sinusoidal alternating current. Curve A, foot muscle of a snail; curve B, sciatic nerve of a frog. (Modified from Coppée: Arch. Int. Physiol. 40: 1, 1934.)

excitation; in fact, in this way it is possible to burn a tissue without causing excitation. Also, constant currents of subthreshold strength can dissipate considerable energy in a tissue without causing excitation. It can be shown that threshold currents having a duration approximately equal to the *chronaxie* (Fig. 7) will produce excitation with a minimum expenditure of energy and thus minimum injury to the tissue. Obviously, in speaking of a threshold stimulus it is necessary to specify both the strength and the duration of the current.

7. The excitability curve for sinusoidal alternating current can be deduced from the excitability curve of Fig. 6, and two such curves are given in Fig. 8.

It will be seen that there is an optimum frequency for stimulation, and it is interesting to note that the 60 cycle electric power so universally used is near the optimum frequency for stimulation of most mammalian tissues and therefore about the most dangerous frequency which could have been chosen. These curves also show that the threshold is very high at high frequencies, and thus a great deal of power can be dissipated in tissues at such frequencies without causing excitation. This fact forms the basis of diathermy machines, electric cauterizers, etc.

Excitability curves can be deduced for a wide variety of different forms of current, and some of these have considerable practical as well as theoretical importance. Katz[6] has recently published an excellent review of the entire subject of electric excitation in nerve.

The shape of the excitability curve of Fig. 6 varies considerably from nerve to nerve and tissue to tissue. The curve reaches a maximum in a fraction of a millisecond for large mammalian nerve fibers, in about 3 msec. (1 msec. = 0.001 sec.) for the frog's gastrocnemius muscle, and in 80 msec. for the turtle heart. As pointed out above, the true threshold value of current is difficult to specify, but under very favorable conditions in single nerve fiber preparations a current of only 2 microamperes is sufficient to cause excitation. In some tissues the excitability returns completely to its resting value during the passage of a constant current (complete accommodation) but in others the excitability does not return at all (no accommodation). In the latter case, if the current is of threshold strength, the nerve will continue to give responses as long as the current flows.

Since the true threshold of a tissue is very difficult to determine (Fig. 5), it is not valid to compare the excitabilities of two different tissues on the basis of threshold measurements. Lapicque[7] has attempted to overcome this difficulty by using the chronaxie of a tissue as a measure of its excitability. *Chronaxie* is defined as the shortest duration of current of twice the rheobasic strength which will stimulate (*C* in Fig. 7). Presumably varying amounts of intercellular fluid would merely shift the strength-duration curve parallel to the current axis without altering its time scale. This is true, however, only to a first approximation. According to Lapicque every excitable tissue has a characteristic chronaxie, and in general it can be said that the chronaxie varies with other physiological properties, such as rate of conduction of the wave of excitation, and speed of mechanical response. Lapicque also developed the "law of isochronism" which states that within a single system such as the nerve-skeletal muscle preparation the chronaxies of the successive parts are approximately the same. The inference is that this is a necessary condition for the transmission of excitation through the system. A tremendous amount of work has been done in which the theories of Lapicque have been applied and tested. Some of his conclusions cannot be accepted. It appears that "isochronism" is by no means a necessary condition for neuromuscular transmission. Davis and Forbes[4] have written an excellent review of this whole subject.

On the basis of the facts of electrical stimulation which were outlined above, many attempts have been made to arrive at a theoretical explanation of the process of excitation. Nernst assumed that excitation takes place when the electric current has caused the accumulation of a threshold concentration of certain ions at some point on the cell membrane. His theory accounted for some facts very well, but failed to account for the existence of a finite rheobase or any of the phenomena associated with accommodation. Lapicque, Hill, and many others have proposed ingenious modifications of Nernst's theory in an attempt to overcome these and other difficulties. None of them, however, has proved satisfactory when tested by all the known experimental facts, and we are forced to admit our ignorance, at this stage, of the intimate nature of the excitatory process.

Within the past few years a number of mathematical theories of excitation have been proposed, the most complete of which was formulated by Hill.[5] Whereas these theories do

not attempt to explain the mechanism of excitation, they do coordinate a wide field of observed facts on simple and easily verifiable assumptions, and give a clearer and more consistent concept of these phenomena. Recently there have been a number of physical measurements on nerve dealing with the electrical properties of the cell membrane and the way in which they change as a result of excitation and current flow. These measurements have so far failed to establish the necessary and sufficient conditions for the initiation of excitation, but they have furnished valuable information which has been used (1) to establish rigid requirements which must be met by any theory of excitation and (2) to give a relatively clear concept of the conduction of the nerve impulse which, as will be shown later (Chapter VII), is intimately associated with the process of excitation.

CHAPTER III

MUSCULAR CONTRACTION

PROPERTIES OF SKELETAL MUSCLE

Voluntary and reflex nervous activity expresses itself in the reactions of the muscles of the body. In order to interpret the normal working of the motor mechanism, and the abnormal manifestations which disease of the nervous system imposes on the muscles of the body, the nature of the contractile processes in skeletal and smooth muscle must first be understood.

The response of a muscle to stimulation may be studied by fixating its origin and connecting its insertion to a lever arranged so as to record its excursions graphically on smoked paper or on a photographic film. Depending on the nature of the lever used, one or the other of two types of contraction, the isotonic or the isometric (see page 29), may be recorded. When records (myograms) of muscular contraction thus obtained are examined, it is found that the unit element to which muscular activity may be reduced is the *simple twitch*. It is the product of a single brief stimulation, such as is brought about by a single induction shock applied to the muscle (direct stimulation) or by a single volley of nerve impulses set up in the motor fibers supplying the muscle (indirect stimulation). The twitch may be divided into three intervals: the latent period, the period of contraction and the period of relaxation. Intimately associated with the mechanical response is an electrical response called the action current or action potential (see page 25) which almost immediately follows the stimulus. As usually recorded it begins slightly in advance of the first indication of the mechanical response and is completed before the contraction has proceeded far (Fig. 9).

The *latent period* is the time which elapses between the application of the stimulus and the first appearance of shortening or the exertion of tension by the muscle. Its duration can be determined accurately only by observing the greatest experimental precautions, and in classroom experiments it is always greatly exaggerated because of the inertia of the recording apparatus. Indeed the values reported for its duration have become progressively less as physiologists have employed more delicate methods of registering the initial phase of the mechanical response. Thus its first determination by von Helmholtz in 1850 resulted in the figure 10 milliseconds (1 msec. = 0.001 sec.) while Roos[23] in 1932, studying the same muscle (the gastrocnemius of the frog) but using the extremely sensitive wire myograph of Einthoven, found latencies as short as 0.4 msec. when the muscle was stimulated directly. He concluded that even these brief periods are due to inability to determine the actual initial movement of the recording lever and that the electrical and mechanical responses begin simultaneously. Snyder,[24] however, by using a special technique obtained evidence that the onset of the mechanical response definitely follows the beginning of the electrical response. The latency of the latter must be very small; in nerve the action potential begins not later than 0.1 msec. after the stimulus is applied, and

this is probably true of muscle. Brown and Sichel[9] in a study of the contractions of isolated single fibers found latencies of from 1.5 to 2.5 msec. When a skeletal muscle is stimulated through its nerve (indirect stimulation), the apparent latency is of course longer and the "true latency" can only be obtained by subtracting the time required for conduction of the volley of nerve impulses to the muscle and for the passage of excitation across the motor end-plates.

The *period of contraction* of an isometric twitch recorded by means of a frictionless myograph begins abruptly about 1.0 msec. after the onset of the electrical response. A very short phase of upward concavity is followed by an upward convexity to the summit (Fig. 9). The *period of relaxation* is formed, first, by a continuation downward of this same upward convexity and, second, by a gradually developing concavity which continues until the resting tension is reached. It is somewhat longer than the period of contraction. The isometric twitch is devoid of any sudden discontinuities. The interval between the beginning of the action current and the attainment of maximum tension (the summit of the isometric myogram) marks the duration of the contraction process and is called the *contraction time*. The contraction times of different skeletal muscles vary considerably, and these differences serve as a basis for a classification of muscles into "slow" and "rapid" types (see Fig. 54, page 133). Thus in the

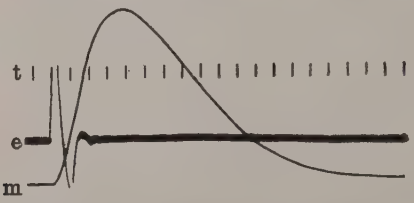

Fig. 9.—Isometric twitch of extensor digitorum longus muscle of cat. Mechanical, *m*, and electrical, *e*, records of the response; *t*, the time record in hundredths of a second. (From Creed, Denny-Brown, Eccles, Liddell, and Sherrington: *Reflex Activity of the Spinal Cord*, The Clarendon Press, Oxford.)

cat the following figures (in milliseconds) were obtained by Cooper and Eccles: soleus, 100; medial head of gastrocnemius, 40; extensor digitorum longus, 40; internal rectus of the eye, 7.5-10. When the muscle is allowed to shorten (isotonic contraction), the contraction time recorded is less than when the muscle develops tension but does not change in length (isometric contraction). It is important, however, to understand that because of instrumental inertia the isotonic record of any rapid contraction is always a very inaccurate reproduction of the true events occurring in the muscle itself.

The All-or-None Law.—The question obviously arises how the force of contraction of the fiber is affected by the strength of the stimulus applied to it. When electric stimuli of varying strengths are applied to a skeletal muscle, the contraction produced by each stimulus is proportional to the strength of the latter until this has become of such strength that the maximal response is elicited (Fig. 10). In cardiac muscle, on the other hand, an entirely different result is obtained, for the weakest stimulus, if it produces any response at all, produces one that is maximal; that is, the height of contraction is the same as it would have been had a much stronger stimulus been applied. We may say that in skeletal muscle the response, as measured by the height of contraction, varies

with the intensity of stimulation, whereas *in cardiac muscle the strength of the response is independent of the strength of the stimulus.* This latter statement is known as the *all-or-none law of the heart.*

Skeletal muscles are composed of large numbers of fibers, each one of which may contract quite independently of any of the others. This may be shown by applying an electric stimulus to a thin muscle, by means of a very small electrode. This technique devised by Pratt[21] permits one to obtain a response which

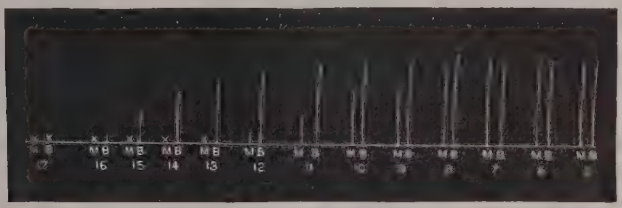

Fig. 10.—Effect of increasing strength of stimulation on the response of skeletal muscle. *M* indicates "make" induction shock; *B* indicates "break" shock; the numbers indicate the distance between primary and secondary coils of the inductorium.

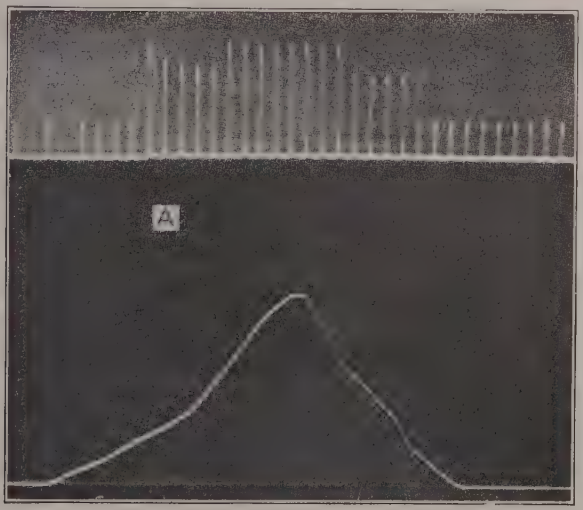

Fig. 11.—The all-or-none nature of the contraction of a single fiber of skeletal muscle. The lower line represents the strength of the stimulus applied to the muscle, which rises to a maximum and then is reduced to its initial level. The upper record is of the movement of a drop of mercury resting on the contracting fiber. The amount of contraction does not change as the stimulus is increased until the point *A* is reached, when a second fiber became excited causing a pronounced steplike increase in the record. Later a third fiber responded and produced another step. The same steps are observed as the stimulus strength is gradually decreased. (From Pratt and Eisenberger.)

is confined to a single fiber. The fibers of the muscle are insulated from one another in such a way that the disturbance set up by the stimulus in one of them does not spread to any other. The unit of function in skeletal muscle is consequently the twitch of the individual fiber, and this raises the question whether the *all-or-none* law may not apply to the contraction of individual fibers. The

first direct evidence of this fact was supplied by the experiments of Pratt and Eisenberger[21] who showed that when a single muscle fiber is excited, its response is maximal if it responds at all. This is shown in Fig. 11 in which the movement of a droplet of mercury placed on a contracting fiber has been photographed. On increasing the strength of the stimulus no change occurs in the amount of contraction until the current strength becomes strong enough to affect an adjoining fiber. At this point the amount of movement increases by a definite step, and then continues at the new level until a third fiber is brought into action and another steplike rise in the record occurs. As the strength of stimulus is decreased again the contractions fall off through the same series of steps. Graded series of muscular contractions in response to graded strengths of stimuli, such as are shown in Fig. 10, are due to the fact that as the stimulus is increased in strength more and more fibers, each contracting maximally, are brought into play until finally all are excited and the contraction of the muscle as a whole becomes maximal and cannot be further increased. The adjustment of the strength and degree of muscular movement consequently depends on bringing into action the proper number of muscle fibers. If the fibers were not insulated from one another graded muscular movements would be impossible and our skeletal muscles as a whole would act in an all-or-none way just as the heart does. In cardiac muscle the fibers are connected together in a *syncytium,* and in consequence, the process of excitation spreads to all the fibers, so that it is impossible to excite a limited part of the tissue without eliciting a response from the whole.

Pratt, and Pratt and Eisenberger[21] used a small pore electrode which delivered an electric stimulus sufficiently local to cause the contraction of a single fiber. In respect to the individual fiber, however, the stimulus was rather diffuse. Gelfan[12, 13] has since shown that when sufficiently small micro-electrodes are used, submaximal responses can be obtained in intact single fibers of the retrolingual membrane and sartorius of the frog. Graded contractions are thus obtained in response to graded intensities of stimulation. Only when the current applied through the minute electrode becomes so strong that, by increasing the area of high density current, it produces a diffuse stimulation of the fiber does an all-or-none type of contraction ensue. The graded responses are due to contractions which involve short segments of the fiber close to the electrode and as the stimulus increases the fiber responds over progressively greater distances (Gelfan and Gerard[16]). These submaximal responses in the single fiber resemble, in their time relations, the ordinary twitch (Gelfan[13]). They differ, however, from the maximal (all-or-none) type of contraction in one important respect; they are not accompanied by an action potential even when partially conducted through the fiber (Gelfan and Bishop[14, 15]). Since the action potential is a *sine qua non* of conduction in nerve (which is all-or-none in character), and since it always occurs in association with the fully conducted maximal response of the individual skeletal muscle fiber it appears to betoken a transmissive mechanism which operates on the basis of the all-or-none law. Under normal conditions of stimulation of the muscle fiber through the large motor end-plate of the nerve the response is evidently of the all-or-none type. Direct proof of this has been obtained by Pratt[20] who could find no trace of submaximal contractions in single muscle fibers stimulated through a single nerve fiber, although these same muscle fibers could be made to yield graded responses when directly stimulated.

Brown and Sichel[9] have obtained further evidence that the single skeletal muscle fiber may, on direct stimulation, show contractions which vary widely in magnitude with the strength of the stimulus. Their preparation consisted of a single fiber dissected from a frog's sartorius or adductor muscle and arranged for isometric recording. When the stimulating electrodes were small the responses produced by weak stimuli were confined to the region under the electrode and typical propagated contractions were rarely obtained. On the other hand, when stimulation was with large electrodes capable of stimulating the entire fiber and so eliminating the factor of propagation of excitation, graded contractions were

obtained. These closely resembled the twitch of a whole normal muscle. The total tension developed was found to vary as a function of the voltage of the stimulating current when the duration was kept constant and as a function of the duration when the voltage was kept constant.

More recently Steiman[25] in Pratt's laboratory has found that in the fresh uninjured preparation the responses of single muscle fibers are always maximal, but that such conditions as absence of circulation, injury and the age of the preparation favor the incidence of local graded contractions. The inference is that the occurrence of the local response depends on an abnormal condition of the fiber. The experiments of Ramsay and Street[22] have thrown further light on this subject. Using single fibers from the frog's semitendinosus they observed three types of responses: (*a*) a typical propagated contraction (twitch) which attains a maximum tension in all-or-none fashion, (*b*) a local twitchlike contraction, the magnitude of which depends on the strength of the stimulating current, and (*c*) a small localized contracture-like shortening which occurs at the cathode, continues as long as the current is applied and is quite distinct from *b*. Strength-duration curves (see page 12) which conform to those for whole muscle were obtained for *a* and *b*. It was found that when the fiber was normal and uninjured gradation of the local twitchlike response was difficult or impossible to observe, since with stimuli of short durations only a propagated contraction of all-or-none type could be obtained and with long durations of current the threshold stimuli for propagated responses were only a few per cent greater than that for the minimum local response and consequently only a very small local twitch was obtained. On the other hand, when the fibers were partially narcotized or slightly injured, all gradations of the local contraction could be observed because at long durations (but not at short ones) the threshold of the all-or-none propagated response was raised far above that of the local contraction. It appears that narcosis or injury by abolishing the propagated contraction or by raising its threshold permits one to observe the gradation of the local twitch with increase in the strength of the stimulus. In view of the facts which are now available it seems fair to state that while the graded local contractions are of interest in the special analysis of the properties of muscle, they do not represent the normally occurring responses of individual fibers of striated skeletal muscle.

Although skeletal muscle fibers *stimulated through their motor nerves* contract to the utmost if they contract at all, it must not be supposed that under all circumstances the maximal contraction is of the same magnitude. The ability of the fiber to develop tension varies from time to time and may be shown to depend on a variety of factors. The energy set free in the contractile process is greater, the longer the muscle at the time when it begins to contract. This is shown by the fact that a muscle which is stretched at the moment when it begins to contract is able to develop a greater final tension than an unstretched muscle. The heat liberated in the act of contraction, which measures the total energy set free, increases in a similar manner with the initial length of the muscle. This observation is of importance because it indicates that the strength of the contraction is related to the surface area of the contractile elements in the muscle fiber, which naturally becomes increased as the muscle is elongated, and not on the volume of muscle substance, which is unchanged by stretching. We shall see in Part III the importance of this principle in enabling the heart to compensate for an increased load by dilating.

Another important fact is that a muscle will develop more energy in a twitch if it contracts against a load, than if it is given no work to do (Fenn effect). The magnitude of the all-or-none output of energy depends not only on the condition of the muscle before it contracts but on the conditions it meets *while* it is contracting.

The previous history of the muscle fibers also has a great influence upon the magnitude of the contractions of which each fiber is capable. If a muscle is

excited to a maximal contraction several times in rapid succession, each twitch is somewhat higher than its predecessor (Fig. 12). This phenomenon is known as *treppe* and is explained by the fact that chemical changes arising from one contraction make the muscle better able to contract the next time. If the successive stimuli are continued for some time, the height of the contractions soon reaches a maximum and then begins to fall off as the muscle becomes fatigued. *Fatigue* is due, in part at least, to the fact that after prolonged activity each fiber in the muscle is able to develop less tension when it contracts.

The Response to Successive Excitations.—If a muscle or its nerve is stimulated twice in such rapid succession that the second stimulus falls during the response to the first, the degree of shortening or the amount of tension developed

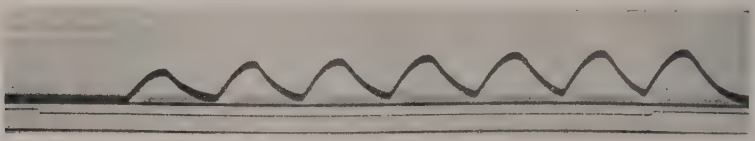

Fig. 12.—The effect of successive stimuli upon the tension developed by skeletal muscle, showing the staircase phenomenon or *treppe*. (From Fulton.)

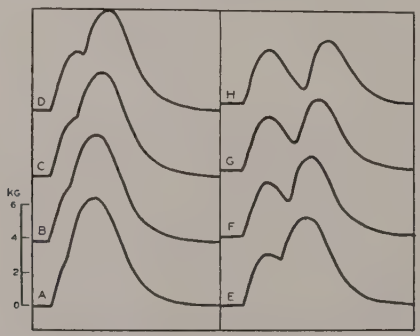

Fig. 13.—The summation of contractions in skeletal muscle. Isometric response of median head of gastrocnemius of cat to two maximal stimuli. Intervals between stimuli in msec.: A, 24; B, 32; C, 40; D, 48; E, 57; F, 69; G, 77; H, 88. (After Cooper and Eccles: J. Physiol. 69: 377, 1930.)

is greater than in the single twitch. This is known as the *summation of contractions*. Since it typically occurs when each of the two stimuli is maximal, i.e., of sufficient strength to excite all the fibers, it is not due to the excitation of a greater number of fibers by the combined stimuli, but to the fact that each fiber contracts with greater force as the result of the second stimulus. The tension of the summated contractions is greatest with the shortest interval between stimuli (Fig. 13). In the case illustrated it is not quite twice that of the single twitch. In certain skeletal muscles, e.g., the internal rectus, the ratio between the tensions of the double response and the twitch may be as high as 3.0.

If a continuous series of rapidly repeated stimuli are sent into the muscle, the result is a prolonged contraction in which the component responses are so completely fused that they cannot be distinguished. Such a maintained response

is called a tetanic contraction, or *tetanus* (Fig. 14). The tension thus developed may be four times that of a simple twitch of the same muscle due to a single stimulus. The frequency of stimulation necessary to produce complete mechanical fusion varies in different muscles and is generally greater the shorter the contraction time. In the cat it is approximately 30 per sec. for soleus, 100 per sec. for gastrocnemius, and 350 per sec. for the very "rapid" internal rectus. If the rate of stimulation is sufficient for summation but not rapid enough to give complete fusion, the myogram shows a partially maintained undulatory plateau called *incomplete tetanus* (Fig. 15). In a complete tetanus all myographic evidence of the repetitive nature of the response is lost; the electrogram, however, shows a series of action currents, one for each stimulation of the muscle (Fig. 14).

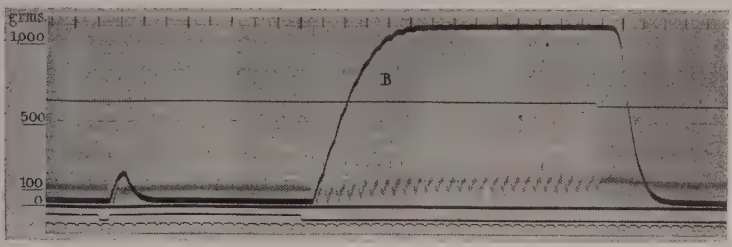

Fig. 14.—A single isometric twitch followed by an isometric "tetanus." The frequency of stimulation is indicated by the action currents recorded dimly above the heavy line marking the mechanical response. (From Fulton.)

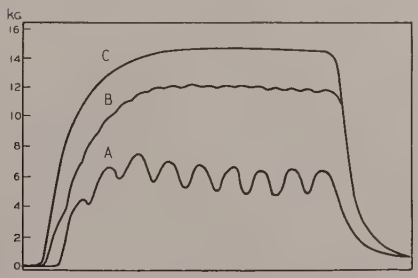

Fig. 15.—Mechanical responses of cat's gastrocnemius to different rates of tetanic stimulation of motor nerve; record A, 19 shocks a second; record B, 35 shocks a second; record C, 115 shocks a second. (Adapted from Cooper and Eccles: J. Physiol. 69: 377, 1930.)

Refractory Period.—If the interval between two stimuli sent into a muscle is made sufficiently brief, summation does not occur. That is to say, the second stimulus, no matter how strong, does not evoke a response. We conclude from this that for a short interval following one excitation, muscle is entirely inexcitable. This period is called the *absolutely refractory period.* It is also found that following the termination of the absolutely refractory period the excitability of the muscle recovers *gradually* so that a stronger stimulus is required to produce summation in the response than is needed to initiate contraction in a resting muscle. This period of depressed excitability is called the *relatively refractory period.* Both refractory periods are common properties of all excitable tissues.

They have been measured with greatest accuracy in the case of nerve and cardiac muscle. The details of these changes as they occur in the frog's nerve fibers are illustrated in Fig. 16.

In cardiac muscle the refractory periods are greatly prolonged. The absolutely refractory period terminates at about the time the muscle is commencing to relax. The relatively refractory period extends throughout the period of relaxation. As a result of this it is only under exceptional conditions that heart muscle is caused to contract again before it has time to relax, and thus the rhythmical nature of the heartbeat is assured. For the same reason cardiac muscle cannot be thrown into complete tetanus.

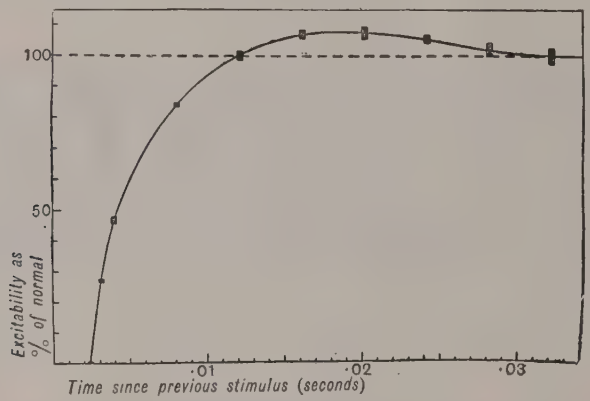

Fig. 16.—The recovery of excitability in the nerve fiber after the passage of a nerve impulse. After a brief time in which no second excitation is effective, the excitability gradually returns to normal, and then becomes temporarily greater than normal. The changes in conductivity following the passage of a nerve impulse over the nerve follow a similar course. (From Adrian and Lucas.)

THE INNERVATION OF SKELETAL MUSCLE

The Motor Unit.—In the intact animal body skeletal muscle normally contracts only in response to nerve impulses transmitted to it from the central nervous system by way of motor nerve fibers. The majority of skeletal muscles are composed of thousands of individual fibers, but each is not supplied by a separate nerve fiber. Instead the axon of each motor neuron splits into many collaterals just before and after entering the muscle and, in the case of mammalian limb muscles, innervates on the average from 100 to 160 muscle fibers.[10] Although each of these can be made to contract independently of one another by direct stimulation, the entire group must respond simultaneously whenever a nerve impulse is set up in the motor nerve fiber. This is because nerve impulses cannot be graded, as will be shown in Chapter VII. The entire motor neuron with its cell body within the central nervous system together with the regiment of muscle fibers which it innervates is called a *motor unit*. Because of the organization of skeletal muscle on the basis of motor units the amount of tension at the command of any one motor neuron may be very considerable. The tension of a twitch or tetanus for a single average motor unit can be determined by dividing the tension of a maximal contraction of the entire muscle by the number of motor axons supplying the muscle. The tetanus tensions

of the average motor unit of several muscles of the cat were found by Eccles and Sherrington[11] to have the following values: medial head of gastrocnemius, 30.1 grams; soleus, 9.9 grams; extensor digitorum longus, 8.6 grams; semitendinosus, 5.5 grams. The twitch tensions are approximately one-fourth of these values.

Gradation of Muscular Contraction: the Two Methods.—The motor unit is the functional unit of all neuromuscular responses involving skeletal muscle, for it is not capable of fractional activity. Nevertheless the number of motor units is great enough to permit a considerable gradation of the contraction of any one muscle. Eccles and Sherrington[11] have shown that approximately 430 motor nerve fibers leave the spinal cord to supply the gastrocnemius of the cat, and it would therefore be at least theoretically possible, by applying finely graded stimuli to the motor nerve, to vary the contraction by 430 steps. It is certainly true that both reflex and voluntary contractions of skeletal muscle may be graded by changes in the number of motor units engaged, i.e., by altering the number of motor neurons which discharge to the muscle. But since the response of the muscle fibers belonging to a single motor unit may be a simple twitch, an incomplete tetanus or a complete tetanus, another means of gradation is possible. We have seen that the amount of tension developed by a muscle varies, inside a limit imposed by the refractory period, with the frequency of stimulation. If the motor neuron of any one unit discharges so slowly that only a series of twitches or an incomplete tetanus is produced, the tension developed by that unit will of course be less than when the discharge is sufficiently rapid to evoke a tetanus. Furthermore, in the former instance the contraction will not be steady. Since voluntary and reflex contractions are usually quite smooth, they were long believed to be invariably tetanic in nature. It is now known, however, that in many cases they are the result of incomplete tetanic contractions of the fibers of individual motor units (see Chap. X). The reason that the contraction of the muscle as a whole is steady is due to the fact that the jerky or undulatory responses of the active motor units are out of phase with one another. Should they become synchronous without a change in frequency the steady pull of the muscle would give way to a tremor or clonus although the tension would average the same. If, however, each active motor unit should be stimulated at a frequency great enough to produce complete tetanus, the tension developed would be the same whether the units were in or out of phase with one another.

CHAPTER IV

ELECTRICAL AND THERMAL PHENOMENA OF MUSCULAR CONTRACTION

In addition to the mechanical effects which are produced in muscular contraction, energy appears in electrical form and as heat. The output of electrical energy is negligible in quantity, but its appearance has given physiologists an invaluable tool in studying muscular activity. The output of heat, on the other hand, is always large and may account for almost the entire energy production of the muscle.

THE ACTION CURRENT OR ELECTROMYOGRAM

That muscles produce electricity when they contract was the conjecture that instigated the famous and productive controversy between Galvani and Volta. Ever since the year 1786 when the former first claimed he had demonstrated the existence of "animal electricity" this subject has figured prominently in the van of physiological progress. Galvani's supposition, so warmly contested by Volta, has become a fact with an application so general that it can now be said of the normal responses of all irritable tissues that they involve a change in potential.

Advance in this field has been dependent on the development of recording instruments sensitive to the small rapidly fluctuating currents set up in living tissue. The early mirror galvanometers could detect them but could not follow their brief course. First, the capillary electrometer, then the string galvanometer of Einthoven, and finally rapidly moving oscillographs were introduced into electrophysiology, and each has added to the accuracy of the results obtained. Even more important has been the advent of the vacuum tube amplifier. This device magnifies small changes of potential of any form, and the output change which may be made very large gives a true reproduction of the input. With such amplification the rapidity of the moving system of the recording instrument has become a more important consideration than its sensitivity. The arrangements for recording electrical changes in muscle or nerve by means of an amplifier and cathode ray oscillograph are shown in Fig. 25 on page 41.

If we connect a recording instrument by means of nonpolarizable electrodes with two parts of a strip of parallel-fibered muscle that has been functionally denervated (e.g., a curarized sartorius of the frog), it will be found that a wave of electrical disturbance is set up whenever a wave of contraction passes over the muscle from one end to the other. The part which first contracts becomes electrically negative to the rest of the muscle but as the wave proceeds the negativity decreases at the end at which it started until, when the wave has reached the middle of the strip, neither end of the muscle shows any potential difference. However, as the contraction wave reaches the farther end of the muscle, this in turn becomes negative (Fig. 17). As a result the curve described

by the deflection of the recording instrument is composed of two limbs. It represents therefore a *diphasic action current.**

No difference of potential can be detected when leads are placed on a resting uninjured muscle or nerve. If, however, the part lying beneath the distal electrode is injured, this portion becomes negative to any point on the uninjured surface. When the two are connected through "leads" of a galvanometer, a positive constant current, which is maintained as long as the tissue is alive, runs in the external circuit toward the injured area. This is called the *current of injury*. It is due to the *resting potential* or potential difference across the cell membrane. If now a conducted wave is set up by stimulation at the proximal end, it will produce, as it passes under the proximal electrode, a momentary negative

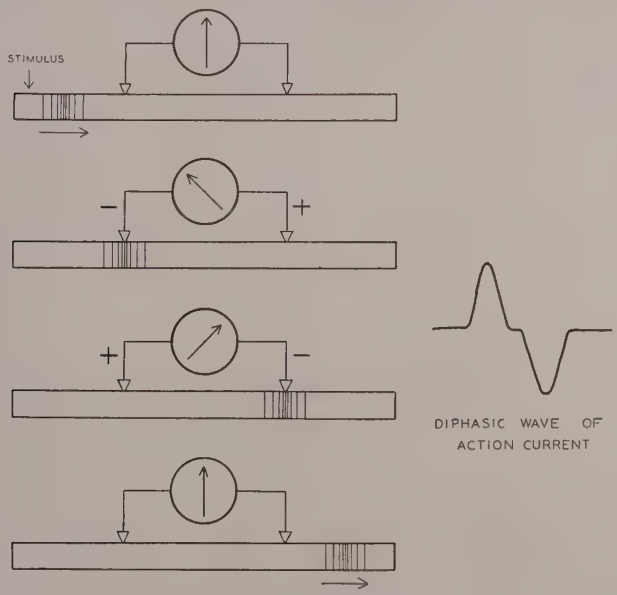

Fig. 17.—A diagrammatic representation of the conduction of the electrical disturbance along a strip of curarized parallel-fibered muscle (or along a nerve). The tissue is stimulated at one end and the resulting wave of electrical activity is shown at various stages as it passes along to the other end (from left to right). As the wave passes under each galvanometer lead, the tissue there becomes momentarily negative in relation to the inactive tissue under the other electrode. The resultant curves as described by the shadow of a galvanometer string are shown at the right. (After Fulton: *Muscular Contraction and Reflex Control of Movement.* Williams and Wilkins Co.)

variation of the constant injury current. As a result the muscle tends to become isoelectric again. The injured region being unresponsive will interrupt conduction of the wave of excitation before it can reach the distal electrode. Consequently the current set up produces a single deflection and the record obtained is that of a *monophasic action current.*

*The terms "action potential" and "action current" are used interchangeably. It should be understood, however, that the former refers to the electric change when recorded by an instrument which draws no current, while the latter is the name for the current which flows through a galvanometer as a result of the change in potential.

The fact that injury and activity give rise to the same electrical condition has led to the inference that the current of injury and the action current are due to the same cause. There is evidence that the surface membrane of a cell at rest is polarized with its outer surface positive to its inner one. The polarity would be destroyed at an injured point, and an electrode placed there would make effective contact with the inside of the cell. The current of injury may therefore be regarded as the result of leading from the inside and outside of the polarized membranes of a group of muscle or nerve fibers. The action current may be explained as the result of a depolarization of the surface of the fibers as the wave of excitation sweeps over them. Fig. 18 illustrates this conception of the action current and its relation to the current of injury.

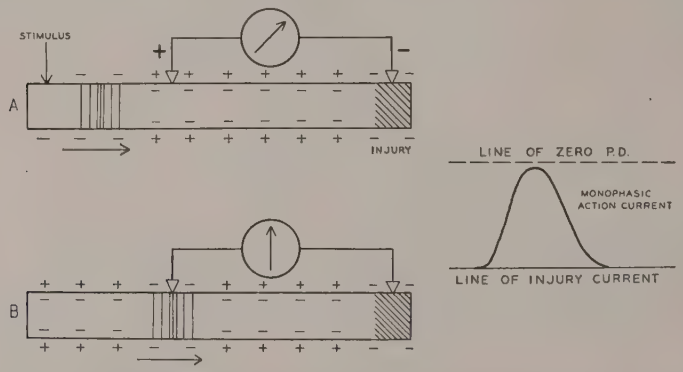

Fig. 18.—A diagram designed to show the source of the current of injury (A) and its relation to the action current (B). With one galvanometer lead on an injured area the passage of the wave of negativity gives rise to a monophasic action current (negative variation of injury current), a record of which is shown at the right.

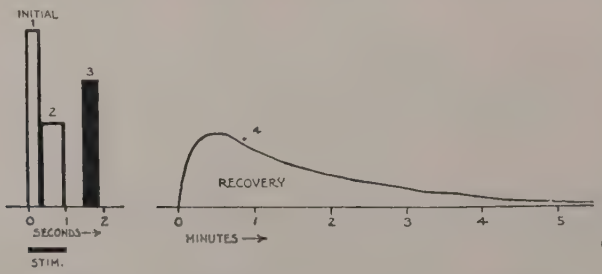

Fig. 19.—A diagrammatic representation of the stages of heat production of muscle during and following a short tetanic contraction. The first three stages represent the initial heat: (1) the contraction heat; (2) the heat produced during the maintenance of contraction; (3) the relaxation heat. The fourth stage is the recovery heat. (From Evans: *Recent Advances in Physiology.* J. A. Churchill, Ltd., London.)

The electrical phenomena in cardiac muscle are of great importance in the study of the heart and in the diagnosis of disorders of conduction in that organ. This subject is discussed in Chapter XXX.

In certain fish effective use has been made of the action currents of muscle. In these animals special structures known as electric organs have been produced

from modified muscular tissues which are capable of generating electrical potentials of several hundred volts, thus forming valuable weapons of offense or defense.

The Heat Production of Muscle.—The contraction of muscle depends upon the occurrence of certain chemical processes within the muscle fibers which yield the energy required for muscular work. This activity leads to the condition of fatigue. In order that the muscles be restored to their original power, other chemical processes must take place which remove the waste products which have developed during activity and replace the chemical materials which have been used up in the period of activity. Both of these chemical processes yield heat. This heat production is of practical utility when we use it to maintain our body temperature, as in shivering or when we exercise to keep warm. On the other hand, it is an inevitable by-product of muscular activity which may render exertion in a hot environment irksome or impossible. It represents energy which is expended without mechanical effect and in this sense is a measure of the inefficiency of our muscles when they are considered as mechanical machines.

The analysis of the heat production of muscle is essential to an understanding of the chemical and mechanical aspects of muscular contraction. It has been made possible by the use of delicate thermoelectric methods of measurement. These depend upon the fact that if two wires of dissimilar metals, such as copper and constantan, are led from a galvanometer and joined together at their ends, any change in temperature at their junction will set up a difference of potential in the two wires and cause a deflection of the galvanometer. By arranging a large number of such junctions in series, very small changes in temperature may be recorded rapidly and with precision. If a muscle is laid across these junctions, the heat produced at any interval during or after its contraction may be determined by analyzing the deflection of the galvanometer. The modern perfection of these methods in physiology is due to A. V. Hill[19] and his associates, especially H. Hartree.

When a muscle is stimulated so that a simple twitch occurs, heat appears in two distinct and almost wholly separable outbursts. The first, which is called the *initial heat,* accompanies the development and subsidence of tension. At the end of the twitch the rate of heat liberation and the tension reach zero at practically the same time. Hartree's analysis[17] of the initial heat of a twitch has shown that it is produced in two phases: (a) the contraction heat which rises and falls off during the development of tension; and (b) the relaxation heat, from 30 to 35 per cent of the entire initial heat, which begins as relaxation sets in and has its maximum when the tension is falling fastest. After the contraction is over, there is a second and slower production of heat, the *delayed heat,* also called the *recovery heat* since it is due to chemical changes which restore the muscle to the condition in which it was before its response. The total delayed heat is about one and one-fourth times the initial heat. When a muscle contracts tetanically, there is a further initial heat production during the maintenance of the contraction. Fig. 19 illustrates the four phases of heat production associated with a short isometric tetanus.

Studies of the relation of oxygen to the heat production of isolated muscle have given results of the greatest significance for an understanding of the mechanism of muscular contraction. The investigations of A. V. Hill and his associates have shown that the time-course and magnitude of the initial heat are essentially the same whether the contracting muscle has been in pure oxygen or has been deprived of oxygen in the most rigorous manner for several hours. On

the basis of this fact it can be asserted with full confidence that the chemical changes which give rise to the initial heat are wholly nonoxidative. On the other hand, the greater part of the delayed heat is dependent on the presence of oxygen. It has been repeatedly shown, however, that in stimulated muscles from which oxygen had been excluded a small delayed heat production occurs after contraction and relaxation. This delayed anaerobic heat is small, amounting, on the average, to about 8 per cent of the initial heat. The chemical processes of recovery which give rise to the delayed heat are, therefore, largely, but not wholly, oxidative in nature. The several phases of heat production associated with a twitch together with their value relative to the initial heat, taken as 1.0, may for convenience be listed as follows:*

Phase	*Relative Value*
(1) Initial heat	1.00
(a) Contraction heat	0.65
(b) Relaxation heat	0.35
(2) Delayed heat	1.24
(a) Delayed anaerobic heat	0.08
(b) Oxygen-recovery heat	1.16

The chemical changes which yield the energy for muscular contraction and which are, of course, the sources of the heat produced by muscle, constitute a special aspect of the subject of metabolism. Accordingly they will be considered in Part V which is devoted to that subject (see Chapter LII).

*It should be understood that the relative values given (see Hartree[18]) are approximate and are derived from results obtained in part when the muscle underwent a series of twitches or a short tetanus.

CHAPTER V

PHYSICAL ASPECTS OF MUSCULAR CONTRACTION

If we are to understand the mechanical problems presented in muscular activity, it is well to begin by considering the muscle as an elastic body. For every length to which a muscle is stretched it will exert a definite tension on its origin and insertion, tending to pull them together until it has returned to its unstretched length. When a muscle "contracts," it does not assume a smaller volume; rather it tends to change its shape so as to become shorter and thicker. The contracted muscle has become a body with new elastic properties, i.e., for each length to which it is stretched, it now exerts a greater tension on its origin and insertion than it did in the "uncontracted" condition. Consequently if opposition is presented to the shortening of the stimulated muscle it will exert a tension on the opposing object (equivalent to the tension necessary to stretch the contracted muscle to its resting length). The muscle's length does not change, and hence it is said to contract *isometrically*. If, however, the opposition is not strong, i.e., is due to a light weight, the tension developed on contraction will overcome the opposition, and the muscle will shorten, thus lifting the weight. Since the weight is the same at all times during the contraction of the muscle, such a contraction is called *isotonic*. When it shortens against a weight the muscle assumes a new length at which it exerts a tension equal to the weight which is lifted. A muscle is consequently a machine which develops tension, and this tension may or may not do work in lifting a weight, or moving a joint, depending on whether or not the tension developed is great enough to overcome the opposition.

When an elastic body, such as a wire, is stretched, its shape is deformed. This deformation is called a *strain* and may be defined as the *percentage increase in length* of the body. The deformation causes forces to be set up between the structural components of the body which tend to oppose further deformation and cause the body to return to its original length when the external force which is stretching it is removed. These internal forces are called *stresses*. The intensity of the stress is measured by the external stretching force divided by the area of cross-section of the elastic body. In the case of a perfectly elastic body the stress is proportional to the strain; that is to say, the more it is stretched, just so much greater is the intensity of the internal forces which oppose the deformation. Furthermore the potential energy of a stretched elastic body is given by the equation:

$$\text{Potential Energy} = \frac{\text{Stress} \times \text{Strain}}{2} \times \text{Mass}$$

While these relations cannot be applied with mathematical exactness to muscle, for reasons to be explained subsequently, the fundamental ideas underlying them are useful in approaching the mechanical problems of muscular contraction. When a muscle contracts, we may think of the chemical changes as setting up *stress* within the structural components of its fibers. If the ends of the muscle are fixed, this stress will manifest itself by putting tension upon the attachments, and this force may be used to measure the stress developed in the muscle. Moreover, the existence of stress implies the existence of a proportionate strain; that is, the fixed muscle is held at a length greater than it would assume if allowed to shorten. If the attachment of one end of the muscle is released, such shortening will occur with the simultaneous disappearance of both the stress and the strain. The degree of shortening may be taken as a measure of the stress which existed in the active muscle before it was allowed to shorten. Knowing the stress and the strain developed in the contraction, one might estimate

the potential energy developed in the isometric contraction; if it were not for certain theoretical and practical difficulties all that would be necessary would be to construct diagrams showing the elastic properties of the relaxed and of the contracted muscle.

The way in which this could be done may be understood by considering Fig. 20. A muscle is suspended from an immovable support, its free end being attached to a powerful spring so arranged that the tension exerted by the spring can be accurately determined. By observing the tensions necessary to stretch the muscle to various lengths, the curve RS may be constructed which describes the elastic properties of the resting muscle. By throwing the muscle into brief periods of tetanic contraction when it is held at each length and observing the tension developed, the curve CT may be constructed which describes the relation between tension and length in the contracted muscle. Such a diagram may be used to illustrate what happens in many of the conditions under which muscles contract. We will consider only the simplest case: of a muscle excited when at its unloaded resting length, OR.

Suppose no weight is attached to the muscle. It will shorten to the length OC. This is an isotonic contraction. Since the muscle is unloaded, the tension (force) it develops is zero and work done is zero; for work = force × distance.

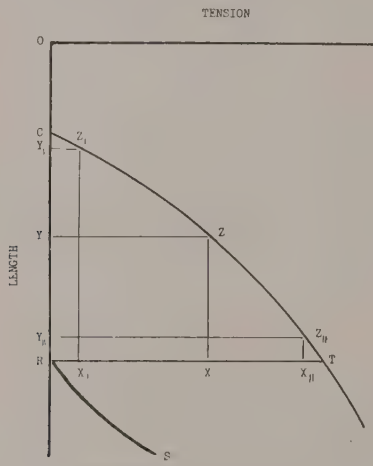

Fig. 20.—The stress-strain diagram of resting and contracted muscle.

Suppose a weight is attached to the muscle, but is so supported that the muscle is not stretched until it commences to shorten. Under these conditions the muscle is said to be *after loaded*. If the weight is very heavy, the muscle will be unable to lift it, or to shorten. The contracted muscle will be held at the length OR, and it will develop an internal stress or tension of RT. This is an isometric contraction. Since nothing is moved, the distance factor in the work equation is zero; consequently an isometric contraction does no work. We can easily estimate from the diagram the potential energy of the isometrically contracting muscle; that is, the total energy stored in the muscle because of its new elastic properties. This may be done by assuming that the potential energy is equal to the work which must be done in stretching the unloaded, contracted muscle from the length OC to the length OR. This work is equal to the triangular area CRT, which consequently represents the potential energy of the muscle in its isometric contraction. Let us now consider how much of this potential energy can be converted into work if the muscle is allowed to lift a weight. Suppose the muscle be after loaded with a weight equal to the line RX. When it contracts, it will shorten through the distance RY. The work done will be equal to the rectangular area RXZY. If the weight be very small, as RX_I, the work done is given by $RX_IZ_IY_I$, which is very small. If the weight be almost sufficient to prevent the muscle from shortening, as RX_{II}, the rectangle representing

the work done. $RX_{11}Z_{11}Y_{11}$, is again very small. These relationships illustrate the fact commonly demonstrated in classroom experiments that as the weight lifted by a muscle is increased, the work done in lifting it passes through a maximum and finally is reduced to zero (Fig. 21).

Unfortunately the contraction of muscle is a more complex affair than the foregoing account might lead one to suppose. It has assumed that in contracting, the muscle goes once for all into a new elastic state and then proceeds to expend the potential energy so developed in work done upon its attachments. As a matter of fact the chemical changes which cause the muscle to contract do not occur instantaneously and entirely before the beginning of shortening, but appear to continue somewhat after the mechanical response has begun. Consequently the conditions under which the muscle responds are able to influence the amount of energy expended during the contraction. The evidence for this is found in the experiments of Fenn (confirmed by Azuma and Hartree) which show that a muscle liberates more energy (measured as heat) if it is allowed to do work by lifting a load than it does in isometric contraction (Fig. 21). The elasticity diagram, of course, takes no account of this additional liberation of energy, being based upon isometric contractions. Its value becomes limited

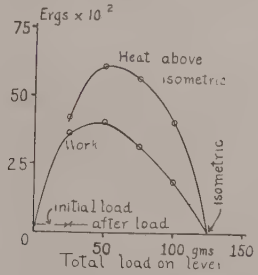

Fig. 21.—Variations of work and heat (measured in units of 100 ergs along ordinate) in isotonic contractions, lifting increasing loads. The heat curve represents only the heat in excess of the isometric heat production, which was 193 × 10^2 ergs. Thus, the isometric heat is made to coincide arbitrarily with the line of zero work. (From Fenn.)

consequently to giving a qualitative picture of the way in which chemical energy can be conceived to give rise to mechanical effects, rather than a quantitative measure of the potentialities of the muscle.

Another difficulty involved in the conversion of potential energy into mechanical work in muscle arises from the fact that if a muscle shortens very rapidly a large fraction of its energy is expended in changing the shape of the muscle, or rather in rapidly rearranging the materials inside the muscle itself. That is to say, a muscle does work against its own "viscosity" as well as against the weight which it lifts. This energy also appears as heat. The importance of muscular viscosity in limiting the speed at which mechanical work can be done by muscle has been demonstrated by Lupton and A. V. Hill.

They arranged a device such that the muscles of the upper arm pulled against a strap wound around a drum which turned a heavy flywheel. With this device, the muscles worked against the inertia of the flywheel which at each moment opposed the shortening of the muscle with a force exactly equal to that which the muscle was capable of exerting. Theoretically, with such an arrangement the entire potential energy of the contracted muscle should appear in mechanical form vested in the kinetic energy imparted to the flywheel. Prac-

tically it was found that this was realized only when the muscles contracted very slowly. If the muscles were permitted to contract rapidly, by winding the strap around a large drum which gave the muscles a great mechanical advantage, very much less work was done in spinning the flywheel. Fig. 22 shows the result of such an experiment. If we designate the theoretical maximal work by W_o and the work actually done as W, it can be shown that

$$W = W_o - \frac{k}{t} W_o$$

That is to say, an increasingly large fraction of the theoretical maximal work is lost in overcoming the viscosity of the muscle substance as the time t occupied in shortening becomes less and less.

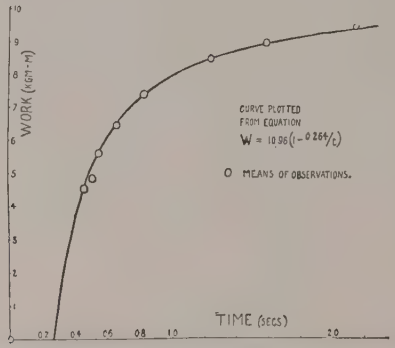

Fig. 22.—Relation between the work done and the time occupied in the movement, in the case of a maximal flexion of the arm. (From Lupton.)

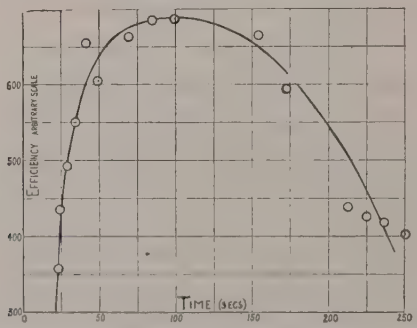

Fig. 23.—Efficiency of stair-climbing at different speeds. The greatest efficiency is reached when each step occupies 1.3 seconds. (From Lupton.)

Speed and Efficiency.—The efficiency of any mechanical process is measured by the ratio of the energy put out in mechanical form divided by the total energy expended in the process. We have pointed out that in muscle the energy which cannot appear as muscular work is degraded to heat and as such can be measured. The efficiency is given by the equation:

$$\text{Efficiency} = \frac{\text{Work}}{\text{Work} + \text{Heat}}$$

In practice the total energy expenditure may frequently be more easily obtained by an examination of the respiratory exchange, from which the energy value

of the chemical processes going on in the muscles may be estimated. It should be clear from the foregoing discussion of muscular viscosity that a muscle does less work if it contracts too fast, simply because a large part of its energy is degraded into heat in changing the shape of the muscle. In the preceding chapter it was pointed out that heat was expended in maintaining the contraction of muscle as well as in producing the contracted state. Consequently more heat is produced if the muscle is caused to shorten slowly through a given distance; whereas beyond a certain point, very little more work is realized by prolonging the time of contraction. It results from these considerations that there is an optimal rate at which any muscular work can be done with greatest efficiency. Fig. 23 shows that there is an optimum speed at which one can climb a given flight of stairs with greatest mechanical efficiency.

The *absolute efficiency* of muscular activity does not exceed about 30 per cent. With this value many machines compare to advantage. The reason muscles are so inefficient is due not only to energy lost in overcoming viscosity in the muscle and in maintaining the contracted state, but also to the fundamental nature of the chemical processes underlying activity and recovery. We have seen that the heat output during activity is somewhat less than the heat produced during the recovery processes. This recovery heat cannot in any conceivable way be converted into mechanical work and consequently is responsible for the largest measure of the inefficiency of muscle.

The Economy of Maintaining Tension.—The economy of energy expenditure in maintaining a muscular contraction can be determined from the tension-time and the heat production. The former is the area under a tension-time curve or $\int Tdt$, where T is the tension, t, the time. If this be divided by H, the heat, the quotient $\int \frac{Tdt}{H}$ may be called the "coefficient of economy of maintaining tension," or simply, the "economy." The economy is of special interest in connection with the mechanism of grading the strength of a muscular contraction of reflex or voluntary origin (page 79). Bronk[8] has shown that as the rate of stimulation of a whole muscle is increased the economy increases. This phenomenon indicates that a weak, steady pull of a whole muscle maintained by a series of asynchronous discrete twitches of the fibers of x motor units is less economical than if the same pull resulted from a complete tetanus of the fibers of x-y motor units. When grading of the tension developed is achieved by a change in frequency of discharge in the active motor neurons, it is apparent that tension is maintained at a smaller expenditure of energy in a strong contraction than in a weak one.

CHAPTER VI

SMOOTH MUSCLE

The smooth muscles of the mammalian body differ markedly in size and in histological appearance from skeletal muscles. Their origin in development is also different, as they arise from the mesenchyme, and not from the mesodermal somites as do the skeletal muscles. It is not surprising consequently to find that the properties of smooth muscle differ, at least in a quantitative way, from those of skeletal muscles. The various musculatures composed of this type of effector play rôles of supreme importance in the mammalian body. The processes of impregnation and parturition depend on the contraction of smooth muscle. The progress of ingested food material through the alimentary canal and its mixing with the digestive juices are wholly dependent on the activities of smooth muscle. Smooth muscle is also a prime factor in the maintenance and regulation of a proper circulation of the blood, and it controls such important things as the amount of light admitted to the retina, the size of the bronchioles, and the volume of the spleen. Obviously there are cogent reasons for inquiring into the functional properties of this ubiquitous effector.

Vertebrate smooth muscle is typically arranged in sheets or layers around hollow viscera, and knowledge of it has been gained from experiments in which the motor activities of such organs have been investigated. In addition, many studies have been made on excised strips of smooth muscle. The more important characteristics which have thus become known are the following.

Motility.—The contraction of smooth muscle is sluggish and never develops very great tension. It is manifested in one or both of two ways. Many smooth muscles exhibit *rhythmic contractions*. These are apt to be slow in development and subsidence, somewhat irregular in sequence and of intermittent occurrence. Perhaps the most outstanding feature of smooth muscle is its peculiar tendency to exhibit a sustained persistent contraction known as *tonus*.* Because of its ability to alter its tonic condition it may exist now at one length, now at another, under equal degrees of tension. This is seen to be a most important property when it is considered that various hollow viscera must frequently alter their capacity to fit the varying volume of their contents. The pressure in the urinary bladder may remain much the same whether its contents be 50 or 150 ml. of urine. Similarly, after injecting 400 ml. of water into the stomach of a dog the pressure within it returns almost immediately to its original level through a change in the tonus of the gastric musculature. The rhythmic and progressive (peristaltic) contractions of the gastric and intestinal walls proceed with equal vigor under widely varying conditions of distention in these viscera. Although some degree of tone is essential for the initiation of the rhythmic activities of

*The nouns "tonus" and "tone" and the adjective "tonic" are used in physiology to signify processes that are, in certain respects, quite dissimilar. Aside from the tonus of smooth muscle we speak of: vagal tone and vasoconstrictor tone each of which denotes a constant, hence "tonic," discharge in specific nerve fibers; the tonus of skeletal muscle which, as we shall see, is due to a fusion of asynchronous incomplete tetani in the fibers of different motor units; and even cardiac tonus which has a less precise meaning and which usually refers to the general condition of the heart. Used unqualifiedly the word "tone" signifies a persistent, rather moderate degree of activity.

the digestive tube, the fact remains that smooth muscle here as elsewhere can do equal amounts of work at different lengths, i.e., when it is in markedly different degrees of tonus.

Smooth muscle responds to a greater variety of stimuli than skeletal muscle. Mechanical, electrical, thermal, and chemical changes are likely to be adequate stimuli. Some smooth muscle, especially that of the gastrointestinal tract and bladder, is readily excited to contract by extension. Rapid extension is always more effective than a slowly induced change in length. Often a mechanical or electrical stimulus which causes contraction when applied to muscle in a state of slight tonic contraction evokes relaxation when the tone is great. Increased acidity causes relaxation and quiescence while increased alkalinity induces a higher degree of tone and more marked rhythmicity. A rise in temperature, as a rule, produces relaxation while cooling causes contraction. Under the influence of excessive acidity and also with rise of temperature to a lethal level (about 50° C.) smooth muscle goes into a fully relaxed state. In contrast to this, skeletal muscle on being gradually heated begins to contract and goes into rigor at 45° C.; acid also tends to cause contraction in this form of muscle. Many drugs and several hormones act on smooth muscle. Of special physiological significance are the autonomic drugs which mimic or interrupt the effects of stimulation of the nerve supplies of smooth muscle.

Excised smooth muscle usually exhibits quite spontaneously the same rhythmic contractions and tonus changes that characterize its behavior in situ. Obviously, unlike skeletal muscle, it is not entirely dependent for its normal excitation upon connections with the central nervous system. But in many organs smooth muscle is intimately associated with nerve plexuses and outlying ganglion cells. For this reason it is sometimes difficult to determine whether any given property of smooth muscle is to be attributed to the muscle itself or to its intrinsic nerves. There is evidence, however, that in the case of intestinal muscle the automatic rhythmicity is myogenic, not neurogenic, in origin. Several investigators (see Alvarez[81]) have observed rhythmic contractions in strips of fibers which were free of ganglion cells. Although some truncated nerve fibers may have been present in these preparations, there is every reason to believe that they could not be the source of rhythmic excitations. Finally, rhythmicity has been seen in isolated smooth muscle cells grown in tissue cultures in which nervous elements are absent. Rhythmic contraction is a property which is by no means limited to smooth muscle. It is the outstanding characteristic of cardiac tissue, a form of striated muscle, and even isolated fibers of skeletal striated muscle will exhibit it under special conditions.

Innervation and Excitability.—The nerve supply of smooth muscle (consult Chapter XI) is peculiar in several respects. First of all, a peripheral neuron is interposed between the central nervous system and the effector. Also, many smooth muscles receive fibers from both divisions of the autonomic system (sympathetic and parasympathetic). In general, where this occurs, the two innervations exert antagonistic effects. For example, in the case of the circularly arranged muscles of arterioles the sympathetic usually causes augmentation of tonus whereas the parasympathetic supply (when present) causes diminished tonus. As a rule, the smooth muscle of the gastrointestinal tract shows increased tonus and rhythmic activity in response to parasympathetic

discharge, relaxation, and stoppage of rhythmicity as a result of activity in its sympathetic innervation. Some smooth muscle, such as that of the hairs (pilomotors), the spleen, the uterus, and the nictitating membrane, possesses a single nerve supply (in these cases sympathetic). There are also wide differences in the degree of dependence of smooth muscle on its innervation. At one extreme is the uterine musculature; it receives a single nerve supply (sympathetic) which exerts no essential control and in many animals appears to cause contraction only during pregnancy. At the other extreme may be placed the ciliary muscle whose finely graded and frequently altered activity (see page 248) is wholly dependent on its innervation.

The histological details of the relationship of nerve fibers to muscle cells are not as well understood in the case of smooth muscle as in that of skeletal muscle. Certain histological studies have suggested that only a fraction of the fibers of some smooth muscles receive nerve endings (see Cannon and Rosenblueth[34]). On the physiological side Rosenblueth and Rioch[36] found not only that a partial destruction of the nerve supply impairs the responses of smooth muscle less than those of skeletal muscle to indirect electrical stimulation, but also that the contractions of smooth muscle are a function of the number of nerve impulses delivered per unit of time, and not of the number of nerve fibers involved. They showed, in the case of the nictitating membrane of the cat's eye, that within reasonable limits stimulation of any small minority of the fibers composing the nerve supply of this sheet of smooth muscle can cause the contraction of a majority of the muscle fibers. Also, Bishop and Heinbecker[27] were unable to evoke local contractions of the radial muscle of the iris on stimulating a fraction of the sympathetic nerve supply. Such results suggest that smooth muscle, in contrast to skeletal muscle, is not organized on the basis of motor units. Because of that organization (see page 22) a given reduction in the number of motor nerve fibers to a skeletal muscle leads to a proportional impairment of the response which can be obtained through nervous channels.

It is probable that among mammalian smooth muscles there are wide differences as regards the ratio of nerve fibers to muscle fibers. For example Clark[35] has demonstrated that each fiber of the ciliary muscle of the cat's eye is intimately related to at least one nerve fiber in its terminal portion, but he is careful to point out that this smooth muscle, which is capable of finely graded contractions, is perhaps a special case and may differ in innervation from other smooth muscles such as those in the walls of the gastrointestinal tract.

The evidence indicating that smooth muscle is not organized on the basis of motor units has been interpreted to mean that it does not obey the all-or-none law. As we shall see (in Chapter XVI) there is every reason to believe that impulses in visceral efferent nerves excite (or inhibit) through the liberation of specific *chemical mediators* (acetylcholine and sympathin) at their terminations. Since these substances are readily diffusible (as shown by their entry into perfusates and blood) an innervation of all the fibers in a smooth muscle is apparently not necessary, for we may suppose that the mediator produced at one nerve ending may act on a number of cells. Now one view (see Cannon and Rosenblueth[34]) holds that, although the responses of the visceral nerve fibers (like those of all nerve fibers—see Chapter VII) are all-or-none in character, the responses of the smooth muscle fibers are graded (i.e., not all-or-none) because the action of the mediator is graded. This concept received

support by several claims to the effect that denervated smooth muscle is electrically inexcitable, a contention which now appears to be either incorrect or of only limited application.

The twin ideas, (1) that large effects may be exerted on smooth muscle through only a few nerve fibers because of diffusion of a mediator, and (2) that the muscle does not obey the all-or-none law because the mediator has a graded action, carry with them the assumption that smooth muscle is not a functional syncytium, i.e., a group of interconnected cells through which excitation can be conducted. Bozler,[31] however, has shown quite conclusively that these concepts are not at all applicable to all smooth muscle, for he finds that certain visceral muscles (ureter and uterus) behave like syncytia and that excitation can be conducted from cell to cell just as in the heart. For example, he found that strips of cats' uterus (if taken from an animal in estrus) respond to electrical stimuli by propagated contractions. Because this uterine tissue does not contain a ganglionated plexus and is innervated by inhibitory fibers, and for other reasons, Bozler's work clearly indicates that the response is not due to stimulation of motor nerves, but to direct excitation of muscle, and is conducted from muscle cell to muscle cell. He was further able to show quite clearly that this type of smooth muscle not only is electrically excitable, but shows a definite strength-duration curve (with very long chronaxie), a definite absolutely refractory period and clearly obeys the all-or-none law. The results of studies[32, 33] of the action potentials of ureteral, uterine, and gastrointestinal muscle are in accord with the conclusion that the properties of the smooth muscle of these organs are not fundamentally different from those of nerve and skeletal muscle. It is not easy, however, to account for the great variety of movements shown by viscera. Bozler[31] has pointed out that different types of motility may be due to quantitative differences in the excitability of various smooth muscles. He has found considerable differences in the refractory phase and in the rate of conduction. In any one smooth muscle these properties doubtless change from time to time and changes in a part of a musculature might cause a wave of contraction to die out or appear to be conducted with a decrement. Further, there is doubtless much difference between the smooth muscle of certain abdominal and pelvic viscera whose nerves are chiefly regulatory and relatively unimportant and the intrinsic muscles of the eye and the muscle of the nictitating membrane which are continually active under the influence of their nerves.

On the basis of the facts available it is premature to attempt a rigorous comparison of the contractions of the skeletal and smooth muscles of mammals and other vertebrates. Certain differences have already been noted. A point which has received much attention is that the tonic contractions of smooth muscle can apparently be maintained with very little increase in oxygen usage or carbon dioxide production and without rapid fatigue. This has led to the impression that smooth muscle in tonic contraction employs some mechanism fundamentally different from that of the tetanus of skeletal muscle. Such an assumption, however, is hardly demanded by the data at hand. In fact recent studies[32] have shown that the tonic contractions of mammalian visceral muscles are accompanied by a continuous discharge of action potentials and are therefore comparable to a tetanus of skeletal muscle. Judged by the accompanying electrical activity the rhythmic contractions of the walls of the stomach and intestines are analogous to recurring tetani of skeletal muscle.[33] Whether this

activity is myogenic or neurogenic in origin is a question which at present cannot be definitely settled; it is one which is irrelevant to the problem under discussion. For a decision as to the energy expended in tonic contraction we must turn to the results of experiments carried out on the smooth muscles of invertebrates. In all probability these results can be transferred to mammalian smooth muscle.

The Properties of Certain Smooth Muscles of Invertebrates.—It should be obvious from the foregoing discussion that the fundamental properties of the smooth muscle of mammals and cold-blooded vertebrates are far more difficult to study than are those of striated muscle. As already indicated, this is due to three facts. In the first place, these smooth muscles when isolated for study tend to maintain a degree of contraction and it is therefore often difficult or impossible to refer induced changes to a resting level or base line. Second, many vertebrate smooth musculatures are arranged in two or more layers capable of contracting independently and with fibers running in different directions. Third, in many organs these smooth muscles contain outlying nerve cells and plexuses and it is often quite impossible

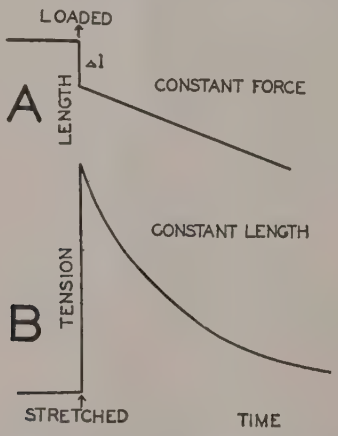

Fig. 24.—Schematic representation of the mechanical properties of the smooth muscle of the retractor muscle of the snail or that of the adductor of *Pecten*. A, extension time curve, showing lengthening after application of a load; *B*, tension changes produced by sudden stretch. (From Bozler: Cold Spring Harbor Symposia on Quantitative Biology **4**: 260, 1936.)

to determine whether any given property is to be attributed to the muscle itself or to its intrinsic nerves. Because of these formidable difficulties investigators bent on achieving a quantitative analysis have turned to certain smooth muscles found among the invertebrates. These effectors, like mammalian skeletal muscle, have a parallel arrangement of fibers, are free from an intrinsic system of nerves and come to rest when isolated. Although they are far removed phylogenetically from vertebrate smooth muscle, study of them has yielded information of interest which on the whole appears to have wide significance.

Mechanical Properties.—One of the outstanding features of smooth muscle wherever encountered is what has been called its *plasticity*. This is a physical characteristic which has been examined quantitatively only in the case of the retractor of the snail's esophagus and the adductor muscle of the bivalve mollusk, *Pecten*. Bozler[29] studied these muscles under two conditions by recording (1) the changes in length under a constant load, and (2) the changes in tension after stretching. The results are diagrammatically represented in Fig. 24. When a load is applied to the resting muscle it first lengthens suddenly and then continues to lengthen slowly (Fig. 24, *A*). In this respect the muscle behaves quite differently from an elastic band or a skeletal muscle. The slowness of the extension indicates a considerable viscous resistance. The highly plastic character of these smooth muscles is brought out even more

clearly by their behavior on being stretched. On suddenly stretching the muscle to a new length it develops tension just as does an elastic band, but if the new length is maintained, the tension, unlike that of a stretched elastic band or skeletal muscle (which roughly behaves like an elastic band) at once drops and disappears within a short time along an exponential curve (Fig. 24, *B*). This latter process has been called "release of tension" to distinguish it from the relaxation of an active contraction. Again it is evident that viscous forces must play an important role in determining the mechanical properties of these smooth muscles. Now Bozler[29] has found that in the case of the snail retractor the release of tension follows the same time course as the relaxation of an isometric contraction; in both cases the fall in tension is affected equally by changing the conditions (e.g., tension of CO_2). Consequently, he concluded that release of tension after passive stretching to constant length and relaxation of contraction are controlled by the same forces, and both are purely physical processes. Furthermore, Bozler[30] has shown that the relaxation heat, which is a considerable fraction of the initial heat, can be wholly accounted for by the release of potential energy stored in the muscle during active contraction. In this muscle the decrease in tension during isometric relaxation is evidently a relatively simple process controlled by viscous forces, whereas in skeletal muscle viscosity is so small that it does not modify the speed of relaxation which in all probability is controlled by some other factor, perhaps a chemical reaction.

The agreement between the time relations of release of tension and of relaxation has led Bozler to conclude that at the beginning of relaxation a contracting smooth muscle is in the same physical state as if it had been stretched. In other words, an active development of tension changes the resting length of the muscle.

While the process of relaxation appears to be quite different in skeletal and smooth muscle, it must not be thought that the contractile mechanisms of the two effectors are fundamentally different. We have already alluded to the fact that the peculiar capacity of smooth muscle to maintain a tonic contraction for long periods without fatigue has led to the suggestion that it operates on the basis of some special and rather mysterious mechanism. It has, for example, been claimed that these tonic contractions are different states of rest, and that only changes from one length to another are active, energy-consuming processes. But this assumption implies that the muscle is a good elastic body, for only such a body could maintain tension at rest without expenditure of energy. As indicated in Fig. 24, the only smooth muscles whose mechanical properties have been studied carefully are quite plastic and do not behave in the least like an elastic band or any other markedly elastic body. Further, as we shall now see, tonic contractions are accompanied by definite expenditures of energy.

Heat Production and Expenditure of Energy.—In comparing energy expenditures in maintained contractions of different muscles the measure of "economy" is the ratio of the tension-time to heat production. It is known that among vertebrate striated muscles those which contract slowly are in this sense more economical than those which contract rapidly, and that less energy is needed to maintain than to develop tension. In smooth muscle the product, tension-time, tends to be high largely because of the prolonged period of relaxation. In a myothermic study of the retractor of the snail's esophagus Bozler[28] found that the "economy" of this rather typical smooth muscle was about thirty times greater than that of frog's striated muscle. The difference corresponds with the difference in time relations. Furthermore, moderate exercise of the smooth muscle made it slower and fifteen times more economical. Bozler calculated that the isolated snail muscle could maintain a tension of 12 grams for one day on the supposition that the glycogen content of the muscle is the same as that in frog skeletal muscle and that this is the source of energy. Such considerations suggest that the differences between the fundamental properties of the two types of muscles are quantitative rather than qualitative. They provide no support for the view that tension can be maintained by smooth muscle without heat production. It is obvious that the low gaseous exchanges reported for tonus of smooth muscle do not signify maintenance of tension without expenditure of energy. In this connection it is significant that in snail smooth muscle, the only smooth muscle as yet subjected to careful myothermic investigation, the heat consists of two parts, the initial heat and delayed heat. The latter is largely, probably completely, absent in the absence of oxygen while the former is anaerobic.

CHAPTER VII

THE NERVE IMPULSE

By Howard J. Curtis

The phenomenon of conduction has been described in connection with striated muscle, but it is most readily studied in pure form in nerve, and since this process forms the basis of all neuromuscular activity, it must be treated before the study of the nervous system as a whole can be undertaken.

Nerve conduction is essentially a matter of transmission of excitation. It is the characteristic response of nerves. Apart from mediating in some undetermined manner the trophic influence exerted by the nerve cell body on all parts of the neuron, the only known function of nerve fibers is to conduct impulses.* Whether stimulated artificially at some point along the course of its axon or normally through a receptor organ or at the region of cell body and dendrites, the neuron responds in precisely the same way—by conduction of a single nerve impulse or a series of impulses. Even in the central nervous system, where complexity of response is so great, there is no known form of propagation of activity other than the nerve impulse. It is indeed "the universal currency of the nervous system" (Sherrington).

CHARACTERISTICS OF ACTIVITY IN NERVE FIBERS

That the unit of response in the nervous system is the nerve impulse conducted by the unit of structure, the neuron, will become increasingly evident in the discussions of the various aspects of nervous activity which follow. An understanding of these topics requires a consideration of the more important characteristics of conduction in the nerve fiber. For the most part, these have been discovered in studies of the responses of peripheral nerve trunks,[44, 47] since it is very difficult to isolate and work with single fibers. In studying the responses of peripheral nerve trunks it is difficult to judge the behavior of the individual fibers, and to do this it is usually necessary to employ indirect methods. Within the past few years several single nerve fiber preparations have been developed, and with the aid of these our knowledge of the nerve impulse has been considerably increased.

Isolated Conduction.—As we shall see, impulses are conducted along a single nerve fiber by a spread of activity from point to point or from segment to segment, but activity does not jump in a lateral direction from one fiber to its neighbor in a nerve trunk or bundle. If a branch of the lumbar plexus is stimulated, contraction occurs in a more limited group of muscles than if the nerve trunk is stimulated below the junction of the various components of the plexus. This simple and easily verified experimental fact alone demonstrates that nerve fibers are functionally insulated from one another. If this were not true, it

*The elaboration of chemical transmitters of excitation (and of inhibition) at the terminals of axon collaterals is an intimately related function (see pages 61 and 177).

would be impossible to grade the contraction of a muscle or to distinguish as separate sensations the touch of two points close together on the skin.

Independent Excitability.—Under normal conditions in the body a neuron is thrown into activity by a stimulus which is transmitted from some sensory end organ or from the collaterals of the axon of some other neuron with which it has synaptic connections. The fibers themselves, however, are so easily stimulated that studies of excitability have, for the most part, made use of isolated nerve trunks or nerve-muscle preparations stimulated through their nerves. As in the case of other excitable tissues, the most harmless and most easily controlled of all artificial stimuli are brief electric currents. The propriety of using this type of stimulus will be realized when it is seen how much reason there is for believing that the normal stimulus for nerves is electrical. When the stimulus applied to a nerve trunk is of threshold value or above, impulses are set up in one or more fibers. If its value is just great enough so that all the fibers are

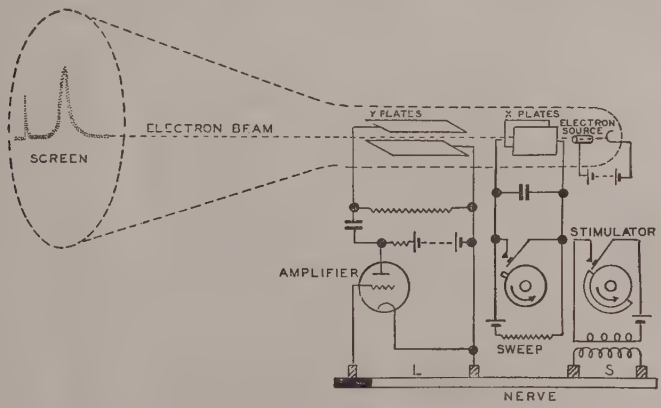

Fig. 25.—Simplified diagram of apparatus used in recording potentials in nerves by means of stimulator, amplifier, and cathode ray oscillograph. In the oscillograph tube an electron source produces an electron beam which is brought to a focus at some point on the fluorescent screen and may be viewed or photographed as a spot of light. A potential difference between the two Y plates causes the spot to shift vertically, and between the X plates horizontally. When the sweep cam opens the key, the spot, starting from the left of the screen, moves to the right at a certain velocity. The stimulator cam, which is mechanically coupled to the sweep cam, opens the stimulator key an instant later, thus stimulating the nerve through the electrodes, *S*, and at the same time creating an electrical disturbance, known as the shock artefact, which produces a small upward deflection of the spot. When the nerve impulse passes the proximal lead electrode, *L*, the amplified action potential causes an upward deflection of the spot which rises to a maximum and then declines. The impulse does not reach the distal lead electrode since it is on a killed portion of the nerve, so the action potential is monophasic. (From Erlanger and Gasser: *Electrical Signs of Nervous Activity*, Philadelphia, 1937, University of Pennsylvania Press.)

stimulated, it is a maximal stimulus for that particular nerve. If it excites less than the total number of fibers, it is a submaximal stimulus. The response to a single electric shock of maximal value or less is a single impulse in each excited fiber. If the stimulus is made definitely supramaximal the excitatory effect may outlast the period of inexcitability that follows the single response and give rise to a second impulse.

It is important to distinguish between the *local excitatory state* induced by the stimulus and the nerve impulse or propagated disturbance. That the two processes differ is indicated by the phenomenon of summation of inadequate

stimuli. Although a single stimulus of subthreshold value fails to set up an impulse, it may leave behind some effect. This is shown by the fact that if two such stimuli are applied in sufficiently rapid succession (less than 1 msec. apart in frog's nerve) excitation occurs. A fleeting change brought about by the first stimulus can apparently be continued and augmented to the point of excitation by the second (see Fig. 6). This change in excitability, or *local excitatory state*, differs from the nerve impulse in several respects: (*a*) it is conducted along the fiber with a very steep decrement, so that the threshold only a few millimeters away from the point of application of the current is not appreciably changed; (*b*) its amount depends on the strength of the stimulus; (*c*) it is capable of summation; and (*d*) it is followed by a relatively but not an absolutely refractory period.

The Action Potential of Nerve.—We have seen how the mechanical response of muscle is accompanied by an action current or action potential. An electric change of precisely the same sort is a universal accompaniment of the nerve impulse. Conduction without an action potential has never been found in

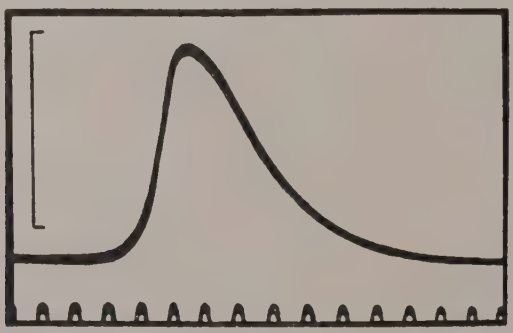

Fig. 26.—Monophasic action potential from a single nerve fiber from a crab. The amplitude of the action potential is 55 millivolts. Time marks 0.1 msec. (From Hodgkin: Proc. Roy. Soc. B. 126: 87, 1938.)

nerves nor does an action current ever arise in resting nerves. Recording the action potential is the best method of detecting the characteristic response of nerve fibers. Although the physiological effects produced by nerve impulses—sensation or a change in some effector—are signs of activity in nerve, they give no direct information about the quality or quantity of the activity. Thermal and chemical changes do occur when nerves become active, but they are more difficult to detect and are so small that they can be measured accurately only when large numbers of fibers conduct many impulses. In contrast, the action potential associated with the conduction of a single impulse along a single fiber can be recorded. Action potentials are the only means of telling exactly when a nerve impulse is passing a given point; they permit one to follow nerve impulses along nerves and central tracts and to measure with the greatest accuracy the velocity of conduction.

An oscillograph record of a monophasic action potential (see page 25 and Fig. 18) of a single unmyelinated nerve fiber is shown in Fig. 26. The duration of this potential is about 1.0 msec., and the velocity of conduction is

4 meters per second; therefore at any given instant about 4 mm. of this fiber is occupied by a wave of negative potential. In the fastest mammalian fibers the duration of the action potential is about 0.4 msec., and the wave is several centimeters long. This wave is known as the *spike potential* or simply the *spike*. The magnitude of the spike shown in Fig. 26 is 55 millivolts, and it is generally believed that all nerve fibers exhibit roughly the same magnitude of potential, although there is very little direct experimental evidence to support this view. The difficulty in making this measurement is that intercellular fluid forms an electrical shunt (see Fig. 5, page 10) on the recording electrodes so that only a fraction (sometimes a minute fraction) of the true potential is measured. For this reason the magnitude of the potential shown in Fig. 26 is unquestionably too small. Quite recently techniques have been developed by Hodgkin and Huxley[65] and by Curtis and Cole[43] for inserting an electrode inside a single nerve fiber from the squid and recording the potential developed across a single active cell membrane. This procedure eliminates the error introduced by the intercellular fluid, and gives a true measure of the action potential. In this way, action potentials of 90 millivolts have been recorded for this nerve.

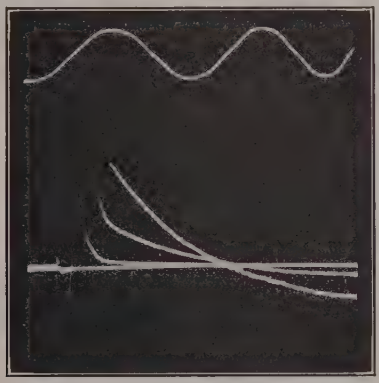

Fig. 27.—Cathode ray oscillograph records showing how the after-potentials are revealed as amplification is increased. Four sweeps were photographed on a stationary film. One, obtained without stimulus, is horizontal and serves as the base line (zero potential). Deflection above this indicates negativity at lead electrode. From left to right, in order of appearance of decreasing negativity, are records of three potentials. In each case the stimulus fell at the same point. In the first of these, the falling phase of the spike can be made out; the negative after-potential can be seen as a continuation of the tail of the spike. In the second, with increased amplification, the spike is too high to be recorded, but the negative after-potential appears as a delayed return to the base line; also the beginning of the positive after-potential is seen in the excursion below the base line. The third record, taken with still greater amplification, shows only the end of negative potential, but now the positive after-potential is brought into prominence. Isolated phrenic nerve of cat at 28° C.; potential recorded monophasically; conduction distance, 72 mm.; spike height, 400 microvolts. Above, time line; 16.7 msec. between crests. (Record obtained by Dr. Wade H. Marshall.)

In recording a monophasic action potential from a uniform nerve trunk it is found that at the end of the spike the potential does not immediately return to the level of the resting potential, but several *after-potentials* can be distinguished. These are ordinarily composed of two parts. The first, which usually appears to be a continuation of the falling phase of the spike, is the *negative after-potential* (Figs. 27 and 28). Under certain conditions (especially after tetanization under veratrine) it can be shown that this potential begins

with a rising phase of its own.[47] In the most rapidly conducting fibers it subsides along a decremental curve for a period of about 15 msec. and then gives way to the *positive after-potential* (Figs. 27 and 28), which normally lasts (in the fastest fibers) about 80 msec. and has a magnitude about 0.2 per cent of the spike height. The positive potential is signalled in records by a deflection below the line of resting potential.

The after-potentials are greatly modified when a series of impulses are set up by repetitive (tetanic) stimulation.[47, 55] At first the maxima of the negative after-potentials are raised, but they soon decline. The falling off is due to the increasing tendency of the nerve to develop positive after-potentials. When the tetanus is stopped, a marked positive after-potential appears at once. With short tetani the depth, but not the duration, of this wave increases (to a maximum) with the frequency of stimulation. After cessation of a longer period of rapid tetanization, the initial positive wave is followed by a second positive component which increases in duration in proportion to the severity of the tetanus (Fig. 29). This second component is definitely distinguished from the first, and may last for as long as five minutes in isolated nerves and one minute in nerves *in situ*. Thus it can be seen that impulses traveling at frequencies comparable to those which actually occur in the body may produce changes of considerable duration. This fact may be of special significance in the central nervous system.

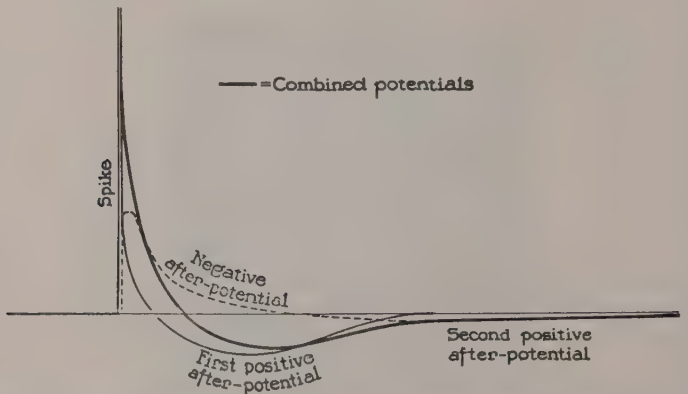

Fig. 28.—Diagram depicting a theoretical series of potentials which summed together would reproduce the action potential of nerve. Two negative parts are shown because of the independence of the spike and the negative after-potential. The positive after-potential is shown in two parts to indicate that following a tetanus this potential is in two parts. (From Erlanger and Gasser: Electrical Signs of Nervous Activity, Philadelphia, 1937, University of Pennsylvania Press.)

The spike possesses great immutability. It always appears when an impulse is conducted, and it is undoubtedly the sign of the nerve impulse itself. The spike and the negative after-potential are separable entities, for under the influence of temperature changes, oxygen-lack, carbon dioxide excess (asphyxia), and changes in pH they manifest strikingly different behavior.[47] It has been found that under anaerobic conditions (Amberson, Parpart and Sanders[37] and others) and after asphyxiation (Lehmann[70]) the after-potentials are depressed to a greater extent than the spike. After some time they disappear entirely so that a somewhat reduced spike is the only electric sign of activity. On restoration of normal conditions (readmission of oxygen) the after-potentials reappear and attain sizes which are greater than those observed in the fresh nerve. This combination of facts suggests that the after-potentials signify an oxidative recovery process. In harmony with this possibility are the results of the effect of veratrine on nerve. It has been found that this drug augments the negative after-potential, increases oxygen-consumption, and leads to greater heat production.[74]

It is regrettable that these after-potentials have never been studied in single fiber preparations, but there can be no doubt that they are inherent properties of single fibers.

However, some recent observations are interesting in this connection. Membrane action potentials from a single nerve fiber from squid[43, 65] show that following the spike the potential immediately swings below the base line, then slowly returns to it. Under some conditions, several positive and negative oscillations were observed before the potential returned to normal. Arvanitaki[38] showed that when this same fiber is bathed in calcium-free solutions oscillations occur spontaneously and may become large enough to reach the threshold and cause self-excitation and thus spontaneous activity. These "after-potentials" are very much faster than those described above. However, Lehmann[68] found in nerve bundles that the negative and positive after-potentials change to very slow oscillations when the nerve is bathed in basic solutions or solutions containing low concentrations of calcium or high concentrations of potassium. How these variations are to be correlated with after-potentials is not entirely clear at the present time.

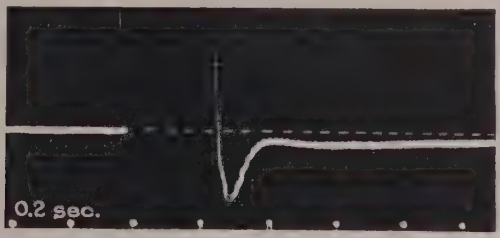

Fig. 29.—Record of after-potentials in phrenic nerve after a long tetanus. The tetanus starts at the break in the line; the amplification is such that the spikes go far above the record and do not appear. The potential is first visible as the negative after-potential and is continued below the base line as the positive after-potential in two parts. (From Gasser: The Control of Excitation in the Nervous System, The Harvey Lectures, 1936-37, Baltimore, 1937, The Williams and Wilkins Co.)

The relationship of the different parts of the action potential to the alterations in excitability which follow excitation in nerve is a subject of great theoretical importance. The latter changes must next be considered.

Excitability Changes Following Excitation.—When two maximal stimuli are applied to the nerve of a nerve-muscle preparation from a frog they may, if separated by the proper time interval, give a summated contraction, and two separate diphasic action potentials may be recorded from leads on the nerve between the point of stimulation and the muscle. But if the interval between the stimuli is decreased to about 1 msec., only a single twitch results and the nerve yields only one action potential. This result is obtained no matter how strong the second stimulus. Evidently a response in nerve, as in muscle, is followed by an *absolutely refractory period.* It is a phenomenon found in all nerves, but its duration is quite different in different types of fibers. In the most excitable mammalian fibers it lasts for about 0.4 msec. The period of complete or absolute inexcitability is followed by a *relatively refractory period* during which it is possible to set up a second impulse, but only by a stronger stimulus than is required to stimulate the resting nerve. During this period excitability increases in the manner shown by the curve of Fig. 16 (page 22). In frog's nerve it reaches a normal level within 7 to 15 msec.; in mammalian A fibers at 37° C., the threshold returns to normal in 3 msec. after the start of the spike potential.

The refractory period is not due to a change which is confined to the point of stimulation. That it actually follows in the wake of the nerve impulse as it passes along the fiber can be shown by applying a stimulus at any point on

the nerve immediately after an impulse set up at a distant point has passed. Here it is found that the refractory periods are of the same magnitude and duration as they are at the stimulating electrode. Furthermore, when two impulses are being transmitted along a nerve in rapid succession, it is found that as long as the second impulse remains in the relatively refractory period of the first it travels at a subnormal velocity.

The absolutely refractory period imposes a limit on the frequency of impulse transmission. The development of the refractory state after each response means that activity in nerves must be discontinuous or rhythmic. Persistent conduction of excitation must be in the form of discrete outbursts like a stream of bullets from a machine gun; it cannot be likened to a continuous stream of water in a hose. As we shall see in subsequent chapters the discharges over motor nerve fibers to skeletal muscle consist of impulses at frequencies which vary, for the most part, from 5 to 50 a second; rarely do they attain a frequency of 100 a second. In sensory fibers the impulses set up by receptor stimulation occur at similar frequencies. The rate of recovery of excitability in the most rapidly conducting and most excitable mammalian fibers is such that it would permit conduction of nearly 1,000 full-sized impulses a second. It is obvious that the properties of these nerves confer upon them a considerable factor of safety for fulfilling their normal function in the body. The refractory period also indicates that after the initiation or passage of an impulse something must be restored before the fiber can act again. Since the absolutely refractory phase has a temperature coefficient characteristic of a chemical process, it is likely that a part, at least, of the recovery of excitability depends on energy derived from chemical changes.

Following the relatively refractory period it is often found that there is a period of *supernormal excitability* during which the conduction velocity is increased.[58] Its duration has been found to be the same as that of the negative after-potential. During the positive after-potential the nerve is in a state of *subnormal excitability*,[59] and there is a corresponding decrease in conduction velocity. Lehmann[68] showed that when the chemical environment of a nerve is changed in such a way as to change the after-potentials, the excitability changes in a corresponding manner. Hodgkin,[63] working with cold and pressure blocks in nerve, showed that whenever the extrinsic potential changed, there was a corresponding change in excitability. It therefore seems quite safe to conclude that whenever a cathodic current flows through a nerve cell membrane the excitability is increased, regardless of the source of the potential causing the current flow. Likewise anodal current decreases the excitability.

All-or-None Nature of Conduction.— It is pertinent to inquire what is the source of the energy expended in the conduction of a nerve impulse. It was perhaps natural to assume that this energy is derived from the stimulus, much as the energy of a projectile is derived from an explosion. That this cannot be true is strongly implied by two facts already discussed: the existence of a threshold for excitation and the development of a refractory state. That the energy for the nerve impulse, once it is set up, is entirely independent of the energy of the stimulus has been indicated by experiments of various kinds.

The most satisfactory measure we possess of the intensity of an impulse as it passes along a nerve is the magnitude of the action potential. In single nerve fibers it can be shown that the magnitude of the action potential is inde-

pendent of the distance from the stimulating electrodes. If there is an injury in the fiber at one point which decreases the action potential there but allows the impulse to pass, the potential regains its normal size after passing the injured point.[75] This phenomenon, first conclusively demonstrated by Davis, Forbes, Brunswick, and Hopkins[45] for the passage of impulses through a narcotized portion of a nerve bundle, shows that the size of the nerve impulse in any particular portion of the fiber depends solely on the condition of that portion. This means that if a fiber conducts an impulse at all, it will be of the maximum strength possible for the condition of the nerve at that time.

The importance of the conclusion that the energy of the nerve impulse is derived from the nerve fiber itself is this: No matter in how complex a fashion an axon may be subdivided into collaterals, an impulse set up in it may pass with undiminished intensity along each of these subdivisions. Since each collateral may be functionally united with other neurons, the impulse may spread from one neuron to many others without becoming attenuated by the multiplicity of the paths in which it is traveling.

Antidromic Conduction.—Within the single nerve fiber, impulses may travel in either direction along its length irrespective of the direction in which conduction normally takes place. Thus if a collateral of a motor neuron is stimulated close to its termination in a muscle, one impulse will travel down to the muscle fibers innervated by that collateral while another will travel up the collateral to spread to other collaterals and so produce activity as widespread as when the unbranched axon is stimulated. Two impulses traveling in opposite directions cannot pass through one another to continue on their respective paths. When each comes into the refractory period of the other it enters inexcitable tissue and is wiped out.

Classification of Nerve Fibers.—Nerve fibers have long been divided into two general classes, namely, *myelinated* and *unmyelinated* fibers. The former consists of an *axis-cylinder* surrounded by a relatively thick *myelin sheath*. In the periphery each myelinated fiber is surrounded by a neurilemma sheath, and both neurilemma and myelin sheaths are interrupted at regular intervals along the fiber, forming constrictions known as *nodes of Ranvier*. In the central nervous system myelinated fibers have no neurilemma sheath and no nodes. Unmyelinated fibers have no myelin; in the central nervous system they are simply naked axis-cylinders but in the periphery they are surrounded by a very thin neurilemma sheath.* In the vertebrates, myelinated fibers are larger and conduct impulses faster than unmyelinated fibers, but in the invertebrates unmyelinated fibers have been found nearly a millimeter in diameter.

Since different fibers conduct impulses at vastly different velocities, this quantity can be used further to classify fibers. By means of a cathode ray oscillograph (Fig. 25) the time interval between the arrival of the impulse at two different points along a nerve may be measured, and, knowing the distance between the points, the velocity may easily be computed. Nerve bundles are composed of many fibers which may have quite different conduction velocities, so velocities measured in this way represent an average for all the fibers in the nerve.

*Schmitt[78] has recently claimed that "unmyelinated" fibers have a very thin myelin sheath. This, however, is irrelevant for purposes of classification.

When a nerve is stimulated with a maximal shock, impulses in the fastest fibers will soon outdistance the slower ones, like runners in a race, and the greater the conduction distance, the greater the distance between them. Then if the action potential is recorded some distance from the stimulating electrodes, it should not be a smooth curve but should show waves indicating the arrival of impulses in fibers of different velocities. It has been found that under the conditions usually employed for electrical stimulation, the threshold for the fast fibers is lower than that for the slow ones. Consequently, when recording some distance from the stimulating electrodes, the wave shape can be varied depending on the strength of the stimulus (Fig. 30). By employing such methods Erlanger and Gasser[46] found that fibers can be grouped into three classes according to their conduction velocities. Fibers of highest velocity

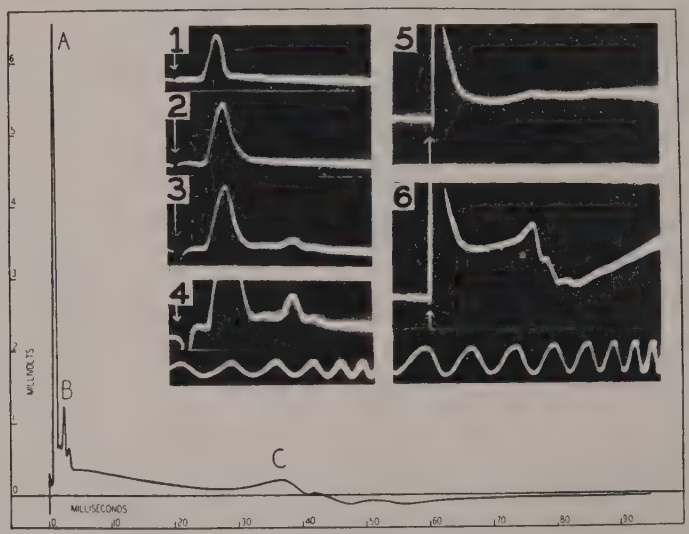

Fig. 30.—*At left and below:* curve plotted to show the three major elevations of the action potential of the saphenous nerve of the cat. The constituent elevations are all drawn to their proper potential and time relations from the cathode ray oscillograph records (*1-6*) shown in the inset. *Inset:* six records showing action potentials recorded when impulses have been conducted 5 cm. from the point of stimulation. *1, 2, 3, 5, 6,* produced by shocks of increasing strength; *1,* fastest fibers of *A* elevation only; *2,* whole *A* elevation; *3, A* and *B* elevations; *4,* same as *3* but at higher amplification to bring out the *B* elevation. Time for *1, 2, 3,* and *4,* 1,000 cycles per sec. *5,* at threshold of the *C* elevation; *6, C* elevation maximal. In *5* and *6* amplifications are 10 times that used for records *1-3;* time 60 cycles per sec. Time of stimulation shown by arrows. (Modified from Gasser: Chapter II in Sensation, Its Mechanism and Disturbances. Baltimore, 1935, The Williams and Wilkins Company.)

are called A fibers; those of intermediate velocity, B fibers; and the slowest, C fibers. Since that time a great deal of work has been done to correlate the structure and function of these fiber groups with their velocity. In general it can be said that (a) those in the A group are large myelinated fibers which innervate skeletal muscle and mediate afferent impulses from proprioceptive receptors in skeletal muscles and tactile receptors in the skin; (b) those in the B group are small myelinated fibers found chiefly in the preganglionic nerves of the autonomic system and postganglionic ciliary nerves; (c) those in the C group are unmyelinated fibers and are found as pre- and postganglionic sym-

pathetic fibers and as afferents mediating sensations of pain and temperature. Gasser[53] has written an excellent review of this subject.

The existence of a wide variation of conduction velocities raises the question as to what are the properties of nerve fibers which determine this difference. Gasser and Erlanger[54] claimed that in the A fiber group the velocity is approximately directly proportional to the fiber diameter. Most investigators agree that for fibers of any one group, the fiber diameter is exponentially related to the velocity, but there is no agreement as to the exponent. On theoretical grounds,[71] one would expect the velocity to be proportional to the square root of the fiber diameter for unmyelinated fibers, but no predictions can be made for myelinated fibers. Between fiber groups, there is no relation between velocity and diameter, and it appears that the most potent factor in determining the velocity is the degree of myelination, but how this factor acts to change the velocity is not known.

The velocity of propagation is by no means the only criterion which can be used for classifying fibers. However, most of the other measurable qualities such as after-potentials, duration of the absolutely refractory period, etc., fit rather well into the classification based on velocities. The various groups overlap with regard to certain properties, and as a result a classification has emerged which is based on no single property. The details of this classification, sponsored chiefly by Gasser and his co-workers, is given in Table I. It should be emphasized that the present grouping is based on quantitative and not qualitative differences, and represents a convenient method for estimating the properties of any mammalian fiber when only one or two of them is known.

TABLE I

PROPERTIES OF THREE GROUPS OF MAMMALIAN NERVE FIBERS (FROM GRUNDFEST, ANN. REV. PHYSIOL. 2: 213, 1940)

GROUP	A	B	C
Diameters of fibers, μ	20 to 1	<3	Unmyelinated
Conduction velocity, m.p.s.	100 to 5	14 to 3	<2
Spike duration, msec.	0.4 to 0.5	1.2	2.0
Negative after-potential			
Amount, per cent of spike	3 to 5	none	3 to 5
Duration, msec.	12 to 20		50 to 80
Positive after-potential			
Amount, per cent of spike	0.2	1.5 to 4.0	1.5
Duration, msec.	40 to 60	100 to 300	300 to >1000
Absolutely refractory period, msec.	0.4 to 1.0	1.2	2.0
Period of latent addition, msec.	0.2	0.2	2.5
Order of susceptibility to asphyxia	++	+++	+

Chemical Excitation of Nerve.—It has long been known that changes in the chemical composition of the fluid surrounding a nerve may drastically alter certain of its properties. The action of drugs on nerves is not clearly understood and will not be discussed, but the action of inorganic ions is simpler and gives some insight into the way in which nerve functions. Calcium and potassium ions are particularly important in this regard and relatively small changes in their concentration cause profound changes in the nerve. When a nerve is treated with solutions containing increasing amounts of potassium, it is found that the excitability at first increases but

later decreases and may reach zero.[52] A decrease in potassium below normal tends to decrease the excitability. If a nerve is treated with a calcium-free solution, the excitability increases and the accommodation (see page 11) decreases, so that several responses may be elicited with a single electrical shock. Brink, Sjostrand, and Bronk[40] found that if a single impulse is sent through a region of nerve which has been treated with a calcium-free solution, a number of impulses may emerge. If the treatment with calcium-free solutions is continued, or if sodium citrate is added further to remove the calcium, the nerve may go into spontaneous activity, and discharge impulses at rates of 300 per sec. or more for many minutes (Brink and Bronk[41]). Lehmann[69] found that spontaneous activity is also associated with high values of pH, but he attributed this to a suppression of the ionization of calcium rather than to a direct hydrogen ion effect. An increase in calcium reduces the excitability. Thus conditions affecting the ionic balance of the blood may produce profound changes in the nervous system.

Some recent results of Arvanitaki[38] on single nerve fibers of squid are very interesting in this connection. Here it was found that when the calcium is removed there are local oscillations of the resting potential which increment and decrement, and at times reach threshold to product self-excitation. When enough calcium is removed, self-excitation follows each local oscillation, giving spontaneous impulses at a rate of about 150 per sec. Arvanitaki concluded that nerve function is essentially oscillatory in nature, and that normally in peripheral nerves the oscillations are very highly damped. This concept may be used to correlate several older observations which had never been explained, and needless to say has very important theoretical implications.

Experiments such as these reveal the wide variation possible within the nervous system. Peripheral nerves are required to transmit one, and only one, impulse for each threshold stimulus. A delicate balance exists which keeps the threshold and accommodation of the fibers at the proper values to perform this task. In all probability receptors exhibit the same fundamental characteristics as nerves, and we can imagine the various qualities of nerve modified for the particular function of a given receptor. For example, a constant stimulus applied to a pain receptor will initiate a train of impulses which lasts as long as the stimulus is applied, i.e., there is no accommodation. On the other hand, there is relatively rapid accommodation (adaptation) in tactile receptors (see page 67). These processes in the central nervous system are very poorly understood, but it seems probable that such factors as the summation of inadequate stimuli, refractory period, supernormal excitability, etc., are of fundamental importance in synaptic transmission. The spontaneous activity (see page 238) which has been observed in the central nervous system may be closely related to that found in peripheral nerves under the influence of calcium-free solutions. Thus by a careful study of the properties of peripheral nerve it may be possible to obtain a better understanding of the other parts of the nervous system.

The Mechanism of Propagation. The way in which a nerve transmits its impulse has been a subject for discussion for many centuries, and during the present century speculation has been particularly keen. Among the many theories proposed, those emphasizing the electrical aspects of the subject have been the ones most favorably received. During the latter part of the nineteenth century a theory was evolved by several workers which is known as the *core-conductor theory* or *membrane hypothesis*. This was first put in quantitative form by Cremer in 1899, but the validity of the assumptions involved

could not be proved at that time. Since then, and particularly since 1936, there has been put forward an increasing amount of evidence supporting this theory, and today it is accepted by most physiologists.

According to the core-conductor theory the nerve cell membrane is the seat of an electromotive force which gives rise to the resting potential of the cell (see page 25). Since the potential is the same at all points on the resting cell membrane, there can be no current flow. A threshold stimulus applied at one point on the nerve causes a breakdown of the membrane at that point which locally abolishes the membrane potential. Thus a potential difference is established between neighboring normal regions and this region of breakdown, and local currents are set up. These currents serve as the stimulus which makes the neighboring segments break down, and thus a breakdown spreads along a fiber like a flame along a fuse. But, unlike a fuse, a nerve fiber repairs the breakdown quite rapidly, so that as an impulse is traveling along a fiber only a short stretch is actually broken down at any one time. A diagram showing these local currents in and around a region of breakdown at some instant during the propagation of an impulse is shown in Fig. 31. Presumably an inactive ("killed") end exhibits the same type of

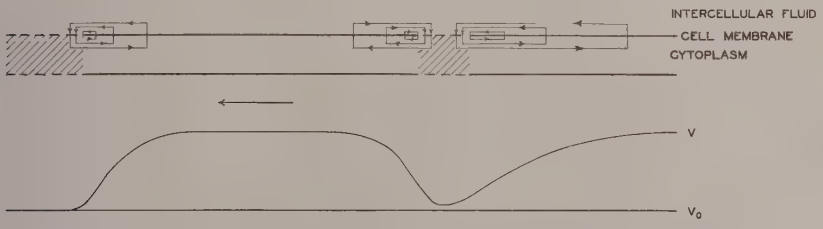

Fig. 31.—Diagram showing current flow in and around an inactive end (left) and the region of breakdown during the propagation of an impulse in a single nerve fiber, according to the core-conductor theory. The shaded areas indicate regions of breakdown. The graph shows the positive potential, *V*, measured along the outside of the membrane relative to that *Vo*, of the inactive end. The arrow indicates the direction of propagation.

breakdown, but there is no recovery. The way in which the local currents and the membrane breakdown give rise to the action potential is also shown in Fig. 31, and from this it is easy to see why the action potential has often been described as the negative variation of the resting potential. As an impulse travels down a nerve the region of breakdown is in an absolutely refractory state, and the region immediately behind this is in a relatively refractory state. This prevents restimulation of the segments behind the impulse.

In order to prove the correctness of this theory it is necessary (a) to show that a membrane potential exists; (b) to show that the current produced by the impulse as it travels down the nerve is sufficient to cause electrical excitation; and (c) to show that when a definite threshold is reached there is a membrane breakdown. The existence of a membrane potential which is measured by the resting potential or current of injury has been known for many years, and probably amounts to about 50 millivolts. The second requirement has recently been satisfied for crustacean (unmyelinated) nerves by Hodgkin[63] and for myelinated fibers by Tasaki.[76] In fact, it has been shown by these workers that there is a large "factor of safety" for self-excitation. The method involved inactivating a short stretch of the nerve by the local application of

cold, pressure, or narcotic, and finding out how much of the nerve had to be inactivated before the impulse would no longer jump the blocked region. The potential due to an impulse arriving at the block was measured just beyond the block, and it was found that when this potential was below the threshold the impulse could not jump the block, but otherwise it could. It was further shown[64, 76] that if a block is produced in a single fiber, conduction can be restored by making an electrical contact around the block. The third requirement has been satisfied by the results obtained by Cole and Curtis[42] in experiments on single unmyelinated fibers from the squid. They showed that during the passage of the impulse the electrical conductance of the membrane, which is normally quite low, suddenly increases by a factor of about 50 and returns to its resting value during recovery (Fig. 32). It will be seen from Fig. 31 that the action potential should start to rise and nearly reach its peak before the membrane breakdown occurs. This postulate was also confirmed (Fig. 32). They further showed that the current which flows through the membrane reverses in direction at the same time that the conductance increases. Fig. 32 shows that the breakdown occurs very rapidly once the threshold is reached,

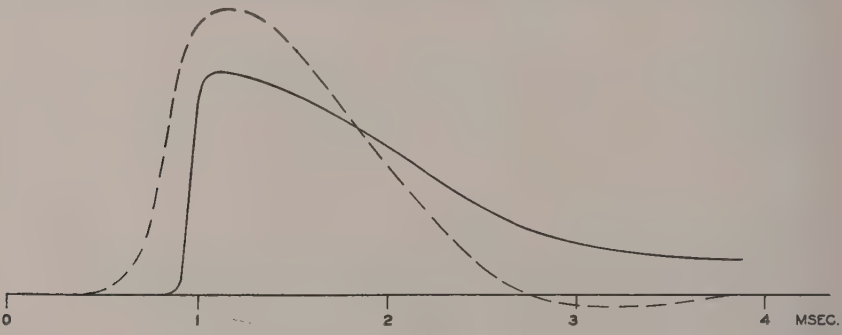

Fig. 32.—Membrane conductance change (solid line) and action potential (broken line) recorded from a single nerve fiber from squid during the passage of an impulse. (From Cole and Curtis: J. Gen. Physiol. 22: 649, 1939.)

and is practically at its maximum value in less than 0.1 msec. The recovery process is relatively slow. Thus a sharp demarcation exists between the region of breakdown and the normal region ahead of the impulse, but no such sharp line exists in the nerve behind the impulse. Whereas the membrane e.m.f. (electromotive force) and conductance change very markedly during the passage of an impulse, this breakdown is far from the complete breakdown which occurs with the death of the cell.

On the basis of these and other facts it is possible to construct a much more exact picture of the mechanism of conduction. It has been found that the cell membrane behaves like an electrical condenser, and thus has a *membrane capacity* which is very high. This membrane capacity does not change appreciably during activity,[42] but it does play a fundamental role in the active process of propagation. It can be imagined that the nerve cell membrane is made up of an infinite number of circuit elements of which three are shown in Fig. 33. This is by no means the only circuit diagram which can be used to explain propagation on the core-conductor theory, and in all probability it is not strictly correct. There have been many such diagrams proposed, but this is the simplest one which can be used to illustrate practically all of the known phenomena of propagation. In the resting state the condensers

are charged but there is no current flow because all elements are at the same potential. If, however, for any reason the membrane resistance and membrane e.m.f. in element A are drastically reduced in magnitude then the condenser in element B will discharge through the external (R_1) and internal (R_2) resistances and element A. The same will be true for the condenser in element C, but to a smaller extent because it must discharge through a higher resistance. When the condenser in element B has become almost completely discharged, the resistance and e.m.f. in element B suddenly become almost short-circuited. The condenser of element C can now discharge more vigorously and thus the impulse is propagated. At any instant the energy required for propagation is furnished by the segments of the nerve ahead of the region of breakdown, and thus the region of breakdown is important only because it furnishes a path for the discharge of the active segments. The breakdown consists in the sudden and simultaneous change of the membrane e.m.f. and conductance, which are closely associated properties of the cell, and these changes constitute the activity which is responsible for the all-or-none law. A part of the energy which is dissipated during propagation in any one segment is restored when the elements on either side discharge into it. In this way there is not as much energy dissipated during propagation as might at first be supposed. The membrane e.m.f. thus plays a relatively minor role in the active process of propagation but is essential for the purpose of recharging the condenser in readiness for the next impulse.

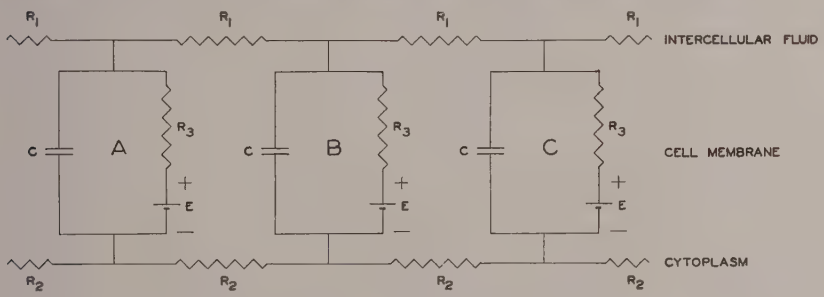

Fig. 33.—A circuit diagram of a single nerve fiber. R_1, external resistance; R_2, internal resistance; R_3, membrane resistance; C, membrane capacity; E, membrane e.m.f.

This theory puts primary emphasis on the cell membrane. Recently Curtis and Cole[43] and Hodgkin and Huxley[65] have succeeded in inserting electrodes through the protoplasm of a single nerve fiber from the squid for a distance of 15 mm. along its axis. After this rather drastic procedure the fiber continued to propagate normally but propagation ceased if the electrode injured the inner surface of the cell membrane. This makes it seem rather unlikely that there is an internal structure in nerve which plays a significant role in the active mechanism of propagation. There is no doubt, however, that the chemical constituents of the protoplasm play a major role in the development and maintenance of the membrane e.m.f. and thus furnish the energy required for propagation. The membrane hypothesis received further support when Hodgkin[64] showed that the velocity of propagation depends on the electrical conductance of the fluid surrounding the fiber, as predicted by the theory.

The picture of propagation which has been presented is based almost entirely on data obtained in experiments on unmyelinated fibers. The simple theory fails to explain the very high conduction velocities found for myelinated fibers. It can be assumed that for myelinated fibers having nodes of Ranvier, the myelin forms an insulating sheath between nodes, forcing the impulse to "jump from node to node." This is an attractive hypothesis and has been supported by the experiments of Kato[67] and Tasaki[76] whose work seems fairly conclusive. It appears, however, to be completely inapplicable to the myelinated fibers of the central nervous system, and it would seem quite surprising if a completely different mechanism of propagation were operative for the two different types of myelinated fibers.

THE METABOLISM OF THE NERVE FIBER

The Heat Production of Nerve.—The fact that the energy for conduction has its immediate origin in the nerve fiber indicates that an increased production of heat should accompany the passage of impulses. A rise in temperature of nerve during activity was for the first time demonstrated in 1926 by Downing, Gerard, and Hill. Subsequently, the heat production of nerves of various sorts has been measured repeatedly with ever increasing accuracy by modifications of the methods used by A. V. Hill and his associates in their myothermic studies.

The average heat production of a resting frog's nerve in oxygen at 20° C. is about 70×10^{-6} calories per gram per second (Beresina[39]). This represents a basal level upon which the heat produced as a result of activity is superimposed. Feng and Hill[49-51] have found that in response to steady stimulation the greatest rate of total heat production, in excess of the basal, is not more than 40×10^{-6} calories per gram per second. This is in striking contrast to muscle which may increase its resting metabolism several thousand fold during maximal activity. The high ratio of the energy used by nerve at rest to that expended when it is giving its greatest response emphasizes an important phenomenon generally found in cells, namely, that energy is required to maintain a state of readiness to respond.

On analogy with muscle it might be expected that nerve would exhibit two distinct phases of heat production, an initial heat associated with conduction and a delayed heat appearing after the response is over. The earlier work on frog's nerve (Downing, Gerard and Hill; Gerard) indicated an initial heat amounting to 11 per cent of the total and showed clearly a second phase which, following the period of activity, continues with a gradual decline for many minutes. The small heat production of vertebrate nerve makes it impossible to record the heat produced by less than about 100 impulses. At ordinary temperatures the time relations of activity are so rapid that it is very difficult to be sure that the first heat which appears during a brief period of stimulation is not in reality heat which arises after impulse conduction. By making the nerves slower by cooling to 0° C. and so increasing the relative speed of the most rapid recording instruments, Hill[61, 62] has shown that heat appears abruptly during stimulation, falls off abruptly at the end of stimulation and, in the case of a short period of activity, may amount to as little as 3 per cent of the whole. This outburst of heat does not lag behind the actual transmission of impulses by more than a fraction of a second and, whether or not it exactly coincides in time with conduction, it certainly constitutes a separate phase of heat production. It may properly be called the initial heat. Immediately after a brief stimulation period, the rate of heat production falls rapidly (end of initial heat) and then more slowly to reach the basal level only after twenty-five to thirty-five minutes. This delayed heat is composed of two phases in point of time: a rapid "A" phase which runs to completion in about twenty seconds and has the same magnitude as the initial heat; and a slow "B" phase which ends after twenty-five to thirty-five minutes and represents the greater part of the total heat. The heat production of nerve is thus different from that of the muscle in that the ratio (initial heat) : (delayed heat) is much less than 1 : 1.25. A more striking difference, however, lies in the fact that in nerve the whole of the delayed heat, not merely a small fraction of it, occurs whether oxygen is present or not.

The absence of oxygen causes the basal heat production of resting nerve to fall off to about 25 per cent of its aerobic level in from three to four hours, after which the output of heat remains constant for many hours. If under these circumstances oxygen is made available, an extra volume of the gas is consumed and extra heat produced. Testing by frequent stimulations shows that at 20° C. frog's nerve remains excitable for several hours after all oxygen is removed. At 0° C. the excitability may last all day and after fifteen hours the total heat response to a stimulation is reduced only 50 per cent. Under these conditions there is a progressive fall in the size, but no change in the distribution, of the excess heat associated with activity. Recovery heat continues, quite unchanged in relation to the initial heat. This is in marked contrast to the behavior of muscle responding under anaerobic conditions.

It is possible to calculate the total heat for a single impulse in a nerve bundle. This has been done by Gerard, Hill, and Zotterman[57] for frog's nerve and was found to be 10^{-6} calories per gram of nerve. Later Gerard calculated from this the total heat per cm. of single fiber per impulse and found it to be of the order of 10^{-12} calories. The total heat per impulse for crab's nerve (unmyelinated) has been found to be about 35×10^{-6} calories per gram.[48] No computation has been made for the heat production per single fiber in crab's nerve, but it seems probable that if this were done the apparently greater heat production in unmyelinated fibers over that of myelinated would be considerably reduced.

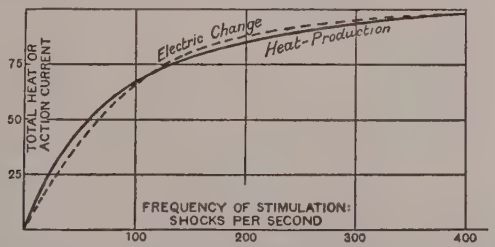

Fig. 34.—Relation between total heat per second (full curve), or total action current per second (broken curve), and frequency of stimulation in shocks per second. The scale of each curve is arbitrary, but the two curves are made to coincide at a frequency of 400. (From Gerard, Hill and Zotterman: J. Physiol. 63: 130, 1927.)

It was found that a close parallelism exists between the total action current and the heat production. This is illustrated in Fig. 34 in which a nerve was subjected to short periods of stimulation of equal duration, but the frequency of the stimuli was varied. As the frequency was increased the heat production instead of increasing linearly, fell off in the same way as did the total action current. It was assumed that at the high frequencies impulses were forced to travel in the relatively refractory period of their predecessors and for that reason were smaller and gave a smaller heat production. However, recent stimulation experiments using single fibers indicate that the height of the action potential is only slightly decreased during high frequency stimulation even though the fiber may not respond to every stimulus (Hodgkin). On this basis, the decreased total action potential would be due to a decreased number of action potentials at the high frequencies, rather than a decrease in the size of each, so that each impulse would expend the same quantity of heat regardless of the frequency of stimulation. However, this explanation is probably not completely adequate, since it seems unlikely that the fibers of these nerves were unable completely to follow frequencies as low as 40 per sec., so the complete explanation will have to await further experiments.

Some results obtained by Feng and Hill[49] should be mentioned in this connection. When a nerve is stimulated at a frequency below 50 shocks per second the rate of heat production rises until in twenty-five to forty minutes it becomes constant and a steady state may be maintained almost indefinitely. At higher frequencies a steady state is impossible; the

heat rate rises quickly to a maximum and then falls off until in a few minutes it is a small fraction of its maximal value (Fig. 35). If now the frequency of stimulation be suddenly reduced, the rate quickly rises again, indicating that "fatigue" in the ordinary sense of the term has not occurred. Once a steady state is attained at low frequencies, turning on a high frequency immediately causes a rapid fall in the rate of heat production. Evidently the response to a low frequency of stimulation so alters the nerve that it gives a lessened response to a higher frequency, although the latter when applied to a fresh nerve always causes, initially, a rise in heat production. It may be possible to explain this striking behavior on the basis of a change in refractory period occurring as a result of conduction. Gasser has pointed out that a study of action potentials reveals the inability of nerve to carry impulses continuously at a rate which is possible for a short period. Temporarily the successive spikes maintain the same height as the second spike, which is determined by its position in the relatively refractory period following the first impulse. Soon, however, they rapidly fall off and the fibers begin to alternate, that is, they fail to respond to every stimulus. This is apparently due to a lengthening of the relatively refractory period as a result of activity. Feng[48] has written an excellent review of heat production in nerve.

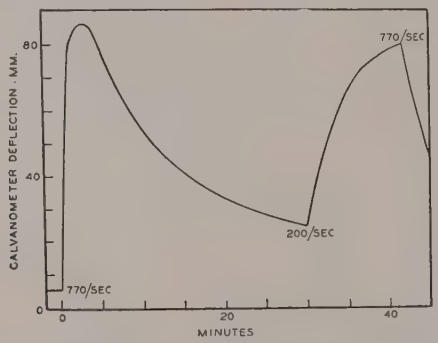

Fig. 35.—Effect of frequency of stimulation of a nerve on the rate of heat production (recorded by galvanometer deflection). Stimulation at a high frequency (770 shocks per second) causes a rapid rise in the rate to a maximum which is not maintained. The subsequent fall in rate is interrupted by a rise when the frequency of stimulation is reduced (to 200 shocks per second). Return to the higher frequency after fourteen minutes produced an immediate fall. (From Feng and Hill: Proc. Roy. Soc. London **113, B:** 356, 1933.)

The Respiration of Nerve.—The importance of oxygen in the metabolism of nerve during rest and activity has already been referred to. The resting metabolism and the excess gaseous exchange of activity may be estimated by determining the oxygen consumption or the carbon dioxide production or both. The metabolism in terms of calories per unit weight may be found by either of these procedures. The oxygen usage may be approximately translated into heat produced even when the fuel burned is unknown, since the ratio of heat produced to oxygen consumed varies by only a few per cent with the type of food substance oxidized. The figures which have been obtained for the resting oxygen consumption of nerve vary considerably, but the better measurements on frog's nerve agree closely in the neighborhood of 42 cubic millimeters per gram per hour. The resting respiratory quotient (R. Q. = volume CO_2 produced : volume O_2 used) lies in the region of 0.8 (Fenn, Gerard). The oxygen consumption of activity over that of rest has been studied in different ways, and the results have varied considerably. Figures close to 15 c.mm. per gram of frog's nerve per hour of stimulation have been secured with some uniformity (Gerard[56]). This average figure is in good agreement with the oxygen consumption to be expected on the basis of the heat production (see Feng and Hill). On the other

hand, Schmitt[72] has recently reported that the carbon dioxide production decreases when a frog's nerve is subjected to low frequency stimulation for short times, but increases if the stimulation frequency is increased above 10 per sec.

The determination of the amount of carbon dioxide which is produced as a result of oxidative processes is beset with difficulties both technical and theoretical. There is general agreement that the extra carbon dioxide output associated with prolonged activity gives an R. Q. which is somewhat higher than that of rest. Generally, such a change would be regarded as an indication that carbohydrate is being used in greater proportion. A given R. Q., however, may be the resultant of a large number of chemical reactions and without direct chemical knowledge of what is going on in nerve it must be used with the greatest caution in determining the kind of foodstuff burned.

In the absence of oxygen a nerve loses its ability to conduct but it does so very slowly. Even after prolonged anoxia (from eight to ten hours) readmittance of oxygen leads to prompt recovery. At rest in the absence of oxygen a nerve continues to produce carbon dioxide and to develop an oxygen debt which may be paid off later. A nerve forced to conduct in nitrogen develops a greater oxygen debt, but produces no more carbon dioxide than a nerve at rest in nitrogen.

The slow loss of function in nerve under anaerobic conditions indicates that much energy remains available for a considerable time after oxygen has been excluded. The relation of the two phases of heat production shows that nerve does not obtain its anaerobic energy in the same way as muscle. It evidently borrows on future oxidations in a different manner. At least two possible sources of the energy for continued anaerobic activity can be made out. First of all, exothermic nonoxidative reactions do occur in nerve (formation of lactic acid; phosphocreatine breakdown). But there is reason to believe that oxidations yielding considerable amounts of energy may take place in the absence of oxygen. It is well known that hydrogen acceptors play an important part in the metabolism and energetics of cells in general. If on reduction one of these cell constituents yields a large amount of energy, it will act quantitatively as well as qualitatively in a manner similar to molecular oxygen and so be of importance to the cell in terms of energy liberation. The operation of such an oxidative system would explain the ability of nerve to withstand anaerobiosis for so long without great diminution of heat output. It is therefore most suggestive that Cohen and Gerard have shown that it is possible to restore an asphyxiated nerve to functional activity by supplying, in place of free oxygen, artificial hydrogen acceptors. Since only those are effective which yield large amounts of energy on reduction it is clear that oxidative recovery depends on the energy made available rather than on the formation or removal of any particular substances. A nerve in nitrogen may therefore be the site of considerably more oxidation than is expressed by its carbon dioxide formation.

Chemical Changes in Nerve.[56]—The carbohydrate metabolism of nerves has received considerable attention. The results of studies of this aspect of the chemistry of nerve form a picture quite different from the one presented by muscle (see Chapter LII). The sugar or free carbohydrate of isolated nerve at rest in oxygen decreases while the amounts of glycogen and lactic acid remain constant. The amount of oxygen consumed indicates that not all the sugar which disappears is burned. On removal of oxygen, lactic acid does appear, some glycogen disappears, and the sugar continues to decrease about as before. The combined breakdown of these substances fully accounts for the increase in lactic acid. Once it is formed, however, lactic acid is not reconverted to its precursors, and it apparently cannot be burned when oxygen is again supplied. This indicates that lactic acid is not an intermediate in the process of carbohydrate oxidation which occurs during rest. Turning to the changes accompanying the extra metabolism

of activity we find that the glycolysis so familiar in muscle does not occur. Thus Holmes, Gerard, and Solomon found that nerves stimulated for periods up to nine hours have the same content of free sugar, glycogen, and lactic acid as their resting controls. These and other results lead to the conclusion that the extra energy required for nerve conduction is not obtained by the oxidation of any of these substances.

Under certain conditions oxidation of lactic acid may occur in nerve.[66] Feng found that a nerve poisoned with iodoacetate fails to conduct in oxygen or nitrogen much more quickly than does a control nerve; both the electric response and the heat production gradually fail, though the curve of heat evolution is not changed in form. Addition of lactate (and oxygen, if the nerve has been asphyxiated) greatly diminishes this effect. Lactate has no effect on unpoisoned nerves. Chang and Gerard then found that the poisoned nerve undergoes a diminution in oxygen consumption and action current from which it can be protected by lactate. Although these results may be interpreted to mean that nerve is capable of utilizing lactic acid by oxidation, it is perhaps wise, in the face of the evidence to the contrary obtained from normal nerves, to suspend judgment until further work has been done. A reasonable suggestion is that although lactate may be burned when other oxidations are interfered with by iodacetate, it is ordinarily not attacked even when present because the oxidative machinery is occupied by more readily available substrates (Gerard).

Phosphocreatine occurs in nerve and is broken down and re-formed as in muscle. At rest in nitrogen this substance breaks down at first rapidly, then more slowly. Stimulation accelerates the process. When oxygen is present, only a small part appears to undergo hydrolysis as a result of prolonged stimulation at frequencies well into the relatively refractory period, and resynthesis occurs during subsequent rest. So far as chemical studies can follow these changes they seem to be slow, but it may be that a very considerable rapid breakdown takes place during conduction and that a rapid resynthesis occurs immediately afterward.

At rest nerve produces a small amount of ammonia and this is slightly increased by stimulation. If the ammonia signalizes a deaminization with complete oxidation of protein, the latter could account for the observed heat and respiration of activity. But it seems more likely that the source of the ammonia is adenyl pyrophosphate which has been identified in vertebrate nerves where it apparently behaves very much as it does in muscle.

These are the major chemical changes which have been found in nerve. The difficulties of chemical analysis are of course great in the case of this tissue, and the rapid time relations of the response make it especially unlikely that the changes closely associated with actual conduction are really reflected either qualitatively or quantitatively in the results that have been obtained. These latter probably represent only the chemistry of the delayed recovery processes which are represented by the delayed heat. At present any attempt to quantitate the chemical with the thermal events is out of the question.

CHAPTER VIII

TRANSMISSION OF EXCITATION AT THE NEUROMYAL JUNCTION

Histologic study shows that in the case of skeletal muscle each collateral of a motor nerve fiber terminates at the end-plate (for details see Fulton[87] and Eccles[85]). The more or less complex and expanded ending of the collateral terminates beneath the sarcolemma of the muscle fiber in a manner which varies in different species. At the region of the ending the substance of the muscle fiber is specialized by a mass of granular cytoplasm in which are embedded many muscle cell nuclei. This nucleated region is the motor end-plate and it is here that the nerve impulse sets up a propagated disturbance in the muscle fiber. There is no certainty of protoplasmic continuity between the hypolemmal nerve terminations and any part of the muscle fiber, but there can be no doubt that the endings make a close and extensive *contact* with the specialized nucleated region of the muscle fiber. The entire structure consisting of nerve terminations and end-plate may be referred to as the *motor end organ.*

The term *neuromyal junction* (or myoneural junction) is often used to denote a functional entity rather than any definite histological structure. This may also be said of the *synapse* which is the name given to the points of contact between individual neurons. In 1850 Pelouze and Claude Bernard discovered that the South American arrow poison, *curare,* blocks transmission from nerve to muscle without destroying the capacity of either to respond to direct stimulation. Later Waller found that "fatigue" induced by prolonged stimulation of the nerve has a similar effect. Obviously both these agencies interfere with the process whereby a motor axon collateral excites a skeletal muscle fiber. The intimate nature of this process is a problem of rather wide interest, for the neuromyal junction closely resembles the synapse. Any information obtained about the mechanism of transmission between motor neuron and muscle fiber is very likely to further our knowledge of synaptic transmission between successive neurons in the central nervous system and in the outlying ganglia of the autonomic nervous system. Both the neuromyal junction and the synapse are differentially affected by fatigue and certain drugs, but their closest similarity lies in the fact that both impose a polarity upon conduction of excitation. Conduction may take place in either direction along a muscle or nerve fiber, but it cannot occur from the former to the latter to set up an antidromic impulse in the nerve. Similarly, at the synapse conduction takes place only from the axon collateral of one neuron to the dendrites and cell body of another neuron.

By means of electrical recording it can be shown that under normal conditions a single impulse in a motor nerve fiber sets up a propagated all-or-nothing response in each of the muscle fibers belonging to that particular motor unit (see page 22). Further, it can be shown that a slight delay, the *end-plate delay,* intervenes between the arrival of the nerve impulse at the motor end-plate and the beginning of the propagated disturbance in the muscle fiber. In the frog's gastrocnemius this delay is about 2 msec.; it averages 1.58 msec. in the sartorius

and 0.82 in the gastrocnemius of the cat;[92] and in the external eye muscles of the rabbit it is normally about 0.7 msec.[88] It follows that whatever may be the process of transmission it is one which occupies a very brief interval of time.

The problem of the mechanism of transmission of excitation from nerve to skeletal muscle is, at the present time, well formulated in terms of two rival theories which are in lively competition with one another. These same two theories also embrace the question of synaptic transmission, but we shall discuss this matter in subsequent chapters (see pages 115 and 120).

The Electrical Theory.—The conception that the action current of the nerve terminal is the adequate stimulus for the muscle fiber was first formulated by Hermann in 1879 and has been emphasized in more recent years by Lapicque, Lillie, and others. According to this view the muscle fiber is stimulated by the local flow of current which is set up as the spike potential reaches the termination of the nerve. In other words this theory simply postulates that the muscle fiber is stimulated in the same way that one segment of a nerve fiber is excited as a result of a membrane change in an adjacent segment. We have seen (page 51) that the current produced by the impulse as it passes along a nerve fiber is adequate to cause electrical excitation; indeed it is sufficient to cause the impulse to "jump" a short segment of depressed or killed nerve. Therefore it has seemed to many quite reasonable to suppose that the action current of nerve reaches across the neuromyal junction and excites the muscle fiber.

The electrical hypothesis is at present chiefly supported by a theoretical extension of the almost universally accepted membrane hypothesis of nerve conduction. Its supporters are quite properly inclined to emphasize the brevity of the end-plate delay. The fact that this interval has a duration of the same order of magnitude as that of the spike potential of the motor nerve fibers is certainly in accord with the theory, and this same fact forces the adherents of the rival theory to pay strict attention to the time element in transmission at the junction. Direct and detailed experimental examination of the electrical theory is fraught with very great technical difficulties and this doubtless accounts for the fact that recent literature on the subject of neuromuscular transmission contains fewer experimental facts which bear on the electrical theory than on the rival chemical theory.

Mention has already been made (page 13) of Lapicque's theory of "isochronism." This hypothesis is based on the assumption that the action current of the nerve excites the muscle electrically. According to this form of the electrical theory neuromuscular transmission is possible only when the chronaxies of nerve and muscle are approximately equal, and a block will be set up if the two chronaxies differ by a ratio of 1:2, a state which Lapicque has termed "heterochronism." Lapicque explains the blocking action of curare by assuming that the poison lengthens the chronaxie of muscle while leaving that of nerve unaltered. The work of other investigators (see Davis and Forbes[4]) has indicated, however, that isochronism is not a necessary condition for neuromuscular transmission, nor heterochronism for blocking by curare. Indeed there is evidence that the electrical excitability of muscle is not altered by small amounts of curare, amounts which are sufficient to block conduction, and it has recently been claimed that curarization may occur without any change in either the magnitude of the nerve spike potentials or the electrical excitability of muscle.[92] If this is true it constitutes very strong evidence against the validity of any form of the electrical theory. It should be remembered, however, that exact measurements of the electrical excitability of muscle are influenced by factors (electrode size, relative position of anode and cathode with respect to responding muscle fibers, the magnitude of the contraction to be used as a criterion of response) which are very difficult to control and which may lead to erroneous conclusions.[4]

The Chemical Theory.—The discovery that postganglionic autonomic nerve fibers which control the activities of glands, cardiac muscle and smooth muscle act through the liberation of specific chemical mediators (see page 177) suggested, but in no way proved, that skeletal muscle is excited in a similar manner. The two autonomic mediators are *acetylcholine* and *sympathin.* Evidence has also accumulated to show that acetylcholine, an active ester of choline) is produced when impulses arrive in the outlying autonomic ganglia (see page 117). This substance may be the means by which synaptic transmission is effected from preganglionic to postganglionic neurons. The local elaboration of these mediators does not normally produce widespread effects in the body, but their presence may be detected by certain experimental means. Thus sympathin entering the blood stream in small amounts at the site of its production causes typical sympathomimetic effects in a distant effector rendered sensitive to it by denervation. On the other hand, acetylcholine is rapidly destroyed by an enzyme, *cholinesterase,* present in all tissues and in blood. This destruction (hydrolysis) is prevented or diminished by the drug *eserine* (physostigmine, prostigmine). In experiments the liberation of acetylcholine as a result of nerve stimulation may be detected by first adding eserine to the blood or to perfusing fluids and then testing for the ester by various pharmacological means.

It has long been known, purely as a curious pharmacological fact, that acetylcholine, when injected intravenously or added to fluid bathing the tissue, may cause in skeletal muscle fibers, especially when they are denervated, slow contractures not preceded by conducted electrical changes. These older observations afforded no basis for the belief that acetylcholine can produce the rapidly developing and rapidly subsiding responses characteristic of skeletal muscle. Dale[82] has pointed out that *if a chemical mediator acts as the direct excitor of skeletal muscle fibers it would have to appear with a flashlike suddenness when an impulse reaches the motor nerve ending, and then disappear within the brief span of the refractory period.*

It was the work of Dale and his collaborators which first provided evidence that acetylcholine may be the transmitter of excitation from motor nerve ending to skeletal muscle fiber. Dale and Feldberg[83] first showed that eserinized perfusion fluid from a skeletal muscle gives various signs of containing acetylcholine when the motor nerve is stimulated. Particularly striking were the results obtained by Dale, Feldberg and Vogt.[84] After removing the sympathetic and sensory nerve supplies to the hindlegs they found that stimulation of the ventral roots led to the appearance of an active substance in the eserinized Locke's solution with which the muscles were perfused. This substance had all the physiological properties of acetylcholine. Although direct stimulation of a normal muscle gave a similar result, no signs of the elaboration of acetylcholine could be detected when such stimulation was applied after degeneration of the motor nerves. Degeneration of autonomic or sensory nerves to the limb did not influence the result of motor nerve stimulation. These results demonstrate that impulses in motor nerves cause the liberation of acetylcholine. The fact that curare does not influence the elaboration of acetylcholine, though it prevents a response in the muscle, indicates that the substance is not produced by the response of the effector cells. Other experiments (Brown, Dale and Feldberg;[79] Brown[77]) have shown that injection of very small amounts (2-20γ) of this substance into the empty artery of a normal mammalian muscle causes a contraction in which the tension develops at not less than half the speed of a maximal motor twitch. Be-

cause of the factor of dispersion one would not expect synchronous activity in all the fibers reached by the acetylcholine. Electromyograms showed that the contractions thus produced are short asynchronous tetani.

If neuromuscular transmission is effected by a flashlike production of acetylcholine, it follows that the effects of nerve stimulation should be enhanced by administration of eserine. Brown, Dale and Feldberg[79] have shown this to be the case. After eserine a single volley of motor impulses produces, instead of a single twitch accompanied by a single action potential, a prolonged contraction with repetitive electrical responses. This result supports the assumption that acetylcholine liberated at the nerve endings in skeletal muscle is rapidly removed (within the refractory period) by a local concentration of cholinesterase. In this connection it is of significance that Marnay and Nachmansohn,[90] Feng and Ting,[86] and Nachmansohn[91] have found that the cholinesterase activity of the innervated portion (end-plate region) of a muscle is three to six times as great as that of the aneural portion. According to Marnay and Nachmansohn[90] and Nachmansohn[91] the local concentration of the esterase at the nerve terminals is several thousand times that in the bulk of the muscle, and they claim that this is sufficient to assure hydrolysis, within the refractory period, of the amount of acetylcholine liberated by a volley of nerve impulses. If this claim is valid it removes one of the greatest of the difficulties which have beset the supporters of the chemical theory.

In view of the older experiments with acetylcholine in which slow contractures unaccompanied by a conducted electrical change were produced by acetylcholine, certain observations by Brown are of interest. He has shown[78] that arterial injections of this substance into normal frog's muscle or denervated mammalian muscle evoke a double mechanical response consisting of a quick initial contraction followed by a slow contracture. The former is accompanied by an outburst of action potentials, the latter by a suppression of the electrical oscillations.

We have repeatedly referred to the action of curare in paralyzing skeletal muscle by interrupting neuromuscular transmission. How can this phenomenon be explained in terms of the chemical theory? It is known that in doses sufficient to produce block, curare does not affect either the course of motor nerve impulses[89] or the liberation of a normal amount of acetylcholine at the neuromyal junction.[84] It appears that this drug raises the threshold of muscle to acetylcholine, for in normally innervated and in denervated skeletal muscle it markedly diminishes the responses resulting from uniform injections of acetylcholine.[79, 95] Thus on the basis of the available evidence the chemical theory appears to give a more definite explanation of the action of curare than does the electrical theory, but it should be borne in mind that the question whether curare does or does not raise the threshold of muscle to an electrical current having the strength and duration of the action current of the nerve terminals has never been satisfactorily answered. The recent demonstration that neuromuscular transmission can be "fatigued" by tetanizing the motor nerve during a curare block is significant. It has long been known that the blocking action of curare is temporary; after a period of paralysis complete recovery, i.e., decurarization, takes place. Luco and Rosenblueth,[89] after giving a cat a paralyzing dose of curare, continuously stimulated the nerve to the soleus muscle of one side at a frequency of 60 shocks a second and from time to time briefly stimulated the nerve to the soleus on the other side to test the degree of curarization. When this test showed that complete recovery from curare had occurred, the muscle whose nerve was being

continuously stimulated was usually not contracting. Since neither the capacity of the motor nerve to conduct (as judged by the spike potentials) nor the excitability of the muscle (as judged by the response of the test muscle) had been affected by the curare, it follows that the fatigue involved the mechanism of transmission. This transmission fatigue can readily be explained on the basis of the chemical theory, if it is assumed that when a prolonged succession of rapidly repeated impulses is set up in a motor nerve the quanta of acetylcholine liberated at the nerve terminals per nerve impulse are reduced until the concentration falls below the threshold level for the muscle.

Other evidence which appears to support the chemical theory and to be very difficult to explain on the assumptions of the electrical theory has been derived from studies of the effects of different rates and periods of stimulation of the motor nerve. Rosenblueth and his associates[94, 96, 97] have distinguished five successive stages of neuromuscular transmission. When high frequencies of indirect stimulation, e.g., 240 shocks a second, are applied continuously over a period of time an initial strong development of tension (stage *1*) is promptly followed by a drop to a low level (stage *2*) which is succeeded within a few seconds by another rise of tension (stage *3*). Then as the high frequency stimulation is continued there is a slow decline in tension to a fatigue level (stage *4*). If the rate of tetanic stimulation of the motor nerve is relatively slow (e.g., 60 a second) the second stage does not appear; the first and third merge and are followed by the phase of fatigue (stage *4*). Now continuance of the stimulation at this rate causes a progressive improvement in performance (stage *5*), and the tension may reach a level as great as 60 per cent of that developed in stage *1*.

The explanation which was given for this complex sequence (see Cannon[80]) was based largely on certain experimental facts: (*a*) that when a nerve is stimulated repetitively there is liberated at first a greatly supraliminal amount of acetylcholine after which the amount per impulse diminishes; and (*b*) that an excess of acetylcholine has a depressant or paralyzing action on skeletal muscle. Stage *1* was attributed to the initial discharge of acetylcholine, stage *2* to accumulation of the excess discharge in paralyzing concentration (without time for destruction by esterase), stage *3* to attainment of an optimal concentration as the excess ebbs away, stage *4* to "fatigue" resulting from a lessened output of acetylcholine which fails to excite some of the muscle cells, and stage *5* to an increase in the ability of the nerve to produce acetylcholine. Since records of the action potentials of the nerve during several hours of stimulation showed no correlation between the sizes of the spikes and the various stages of muscular activity, it appears that these marked changes cannot be attributed to changes in the magnitude of the nerve impulses delivered to the muscle and to that extent cannot be explained by the electrical theory. There is of course the possibility that potentials recorded from the nerve trunk do not represent fair samples of the response of the nerve terminals.

More recent work (Rosenblueth and Cannon[93]) has complicated this picture by revealing the occurrence of another fall in tension in the course of prolonged indirect stimulation of muscle; this is stage *3b*, seen after the rise of *(3a)* which follows stage *2*, and it is in turn succeeded by another rise *(3c)*. The earlier explanation of stage *2* as due to the paralyzing action of excess acetylcholine has been abandoned since injections of acetylcholine during this phase did not cause further depression. The earlier explanation of stage *2*, however, appears to be valid for stage *3b;* addition of acetylcholine produces depression during stage *1* as well as in stage *3b*. Stage *2* was shown not to be a phenomenon of fatigue or exhaustion and it is now attributed to some unknown depressant factor. Rosenblueth, Lissak and Lanari[94] found that the acetylcholine content of motor nerves was low during stage *4*, but gradually increased with the recovery in stage *5*. They interpreted this to mean that stage *4* develops because the output of the transmitter is not adequate to excite contraction in many of the muscle fibers and that stage *5* results when the nerves have become richer in acetylcholine and are liberating more of it. Cannon and Rosenblueth[81] have supplemented this interpretation by finding that eserine augments the muscular response in stage *4* and has chiefly a depressant influence on the response in stage *5*. The protection of acetylcholine by eserine against rapid destruction apparently accounts for these two different effects; in stage *4* there would be an increased concentration at the endings and a larger number of muscle fibers are stimulated, while in stage *5* the concen-

tration becomes so high that it reaches the paralytic range for many of the fibers. There is obviously a nice correlation between these experimental results and the known physiological properties of the presumptive chemical transmitter (acetylcholine). On the other hand, the fact that there is no correlation between the heights of the spike potentials of the stimulated nerve and the development of greater muscular tension as stage *4* passes into stage *5* argues against the electrical theory of transmission.

Summary.—The foregoing discussion of the mechanism of transmission at the neuromyal junction is necessarily a selective account in which only certain significant facts and opinions have been culled from a literature which is full of complicated hypotheses and conflicting facts. It therefore presents a simplified view of the matter and any reader who consults the original literature will find many reasons for being dissatisfied with it.

It may be said that the sum total of available evidence brings strong support to the contention that liberation of acetylcholine is an important factor in the process whereby nerve impulses excite muscle fibers, but it would not be in accord with certain findings to assert that it is the only factor. On the chemical side there is evidence that in some way potassium, which has certain properties resembling those of acetylcholine, may be involved (see Fenn[52]). There are several competent workers in this field who believe that the final explanation will embrace the essential features of both the electrical and the chemical theories. It is, however, not easy at this stage to see how such a reconciliation may be effected. Most of the supporters of the electrical hypothesis, while admitting that acetylcholine is liberated, regard this substance as a mere by-product of nerve metabolism. On the other hand, those who adopt the chemical theory tend to assert, as indicated above, that a number of experimental facts about transmission cannot possibly be accounted for by the electrical hypothesis.

It should be emphasized that we have here been dealing with only one aspect of a general problem which embraces the mechanism or mechanisms of transmission between autonomic nerve endings and visceral effectors and at synapses in the central nervous system and in autonomic ganglia as well as at the junction between nerve and skeletal muscle. It would be reasonable and satisfying to suppose that the same mechanism or mechanisms operate at all four places, but the experimental facts now at hand do not justify such a generalization. While there is almost universal agreement that the immediate control of the slowly acting effectors (glands, smooth muscle, heart) by autonomic fibers is mediated by chemically specific substances (acetylcholine and sympathin) liberated at the nerve terminations (see page 183), the evidence bearing on central synaptic transmission certainly favors the electrical theory (see page 122). We shall see (page 117) that the problem of ganglionic transmission is in very much the same state as that of neuromuscular transmission.

CHAPTER IX

RECEPTOR ORGANS AND DISCHARGES IN SENSORY NERVES

Having reviewed the fundamental conditions of conduction in nerve fibers, we are now in a position to consider the arrangements of neurons which form the basis of the principal aspects of central nervous activity. We will first consider the afferent part of the reflex arc, the activity of which gives rise to the discharge of impulses over motor neurons in reflex activity, and to the phenomena of sensation and discrimination which determine the nature of volitional acts. Disturbances in these arrangements give rise to the sensory symptoms of nervous disease. Such a consideration must start with the study of the receptors or sense organs.

THE EVOLUTION OF SPECIALIZED RECEPTORS

The receptor is a cell specialized in such a way as to be excited by minute changes in the condition of its environment. As a result of such excitation, reflex activity is set up which causes the animal to respond, usually in a way which is to its advantage, and sensations are produced which give information concerning the nature and position of the stimulus and its probable consequences. The primitive type of receptor, which appears in the coelenterates and occurs generally in most invertebrates, consists of an epithelial cell from which a fiber extends into the central nervous system. Such an arrangement persists in the olfactory sense organs in man. With the development of longer nerve trunks in the vertebrate nervous system the cell body is no longer found at the termination of the afferent fiber, but has taken up a position nearer to the central nervous system, in the ganglion of a sensory root. The fibers of such an afferent neuron terminate peripherally in a number of fine branches which extend along the cells of the epithelium, forming a sense organ known as a *free nerve termination*. The sense of pain in man can be definitely associated with receptors of this type. The highest degree of sensitivity cannot be attained by such an arrangement. For this purpose special cells in the skin become modified into receptors, and about these terminate the fibers of the sensory nerves. Thus one cell serves as a receptor, while the other is concerned primarily with conducting the disturbance set up in the receptor to the central nervous system.

Just as a division of labor has been necessary between the receptor and afferent fiber in order that the former may become as sensitive as possible to weak stimuli, so we find a specialization among the receptors, each being adapted to respond to some particular kind of physical or chemical change in its surroundings. Thus we may classify receptors with respect to the stimuli to which they respond most readily. We may speak of chemoreceptors which respond to chemical changes (taste, smell), tangoreceptors which respond to pressure (touch), photoreceptors which respond to light (vision), phonoreceptors which respond to sound (hearing), and calororeceptors which respond to temperature changes (heat and cold). This does not mean, however, that these sense organs

respond only to the type of stimulus to which they are especially attuned. Pressure upon the eyeball may stimulate the retina, an electric current may give rise to the sensation of taste, a temperature of 45° C. will excite the sense organs not only of heat but of cold and pain. But in the latter case, for example, the heat receptors alone are responsive to temperatures between 45° C. and the temperature of the body. *The characteristic of the specialized receptor is that its threshold is much lower for one type of stimulus than for any other.*

A useful and instructive classification of sense organs is that proposed by Sherrington. It divides the receptors into three general types: (1) *interoceptors,* or visceral sense organs; (2) *exteroceptors,* or somatic receptive organs responding to stimuli, such as touch, light, sound, odors, which arise outside the body; (3) *proprioceptors,* sense organs found in muscles, tendons, and joints, which are stimulated mechanically by movement, tension, weight, etc. We may properly include in this third group the two parts of the nonauditory labyrinth—the otolith organs, which respond to changes in position of the head, and the semicircular canals, which are stimulated by movements of the head.

DISCHARGES FROM SENSE ORGANS AND THE INTENSITY OF SENSATION

From what has been related in Chapter VII it is evident that the only messages which can be transmitted from receptors to central nervous system are discontinuous propagated disturbances which do not vary in intensity with the size of the stimulus. Such, at any rate, is the conclusion forced upon us by the results of experiments on isolated nerve trunks containing both motor and sensory fibers and subjected to electrical stimulation. It follows that the only way in which sensory messages from a given receptor can be made to vary is by a change in the number and frequency of nerve impulses set up by the sense organ. Proof that this is actually the case has been secured in great abundance by Adrian[98] and his collaborators in a series of studies of the action currents in sensory fibers which appear when receptors are stimulated. Almost all ordinary sensory stimuli involve many sense organs and so set up independent impulses in many nerve fibers. Because of the resulting asynchronous activity it is virtually impossible to determine the context of the messages carried along individual fibers by recording the summated action potentials from a nerve trunk. This difficulty has been overcome by employing special methods which permit the recording of impulses set up in a single fiber when a single receptor is stimulated.

Among the first discharges from single receptors to be studied was that in a unit consisting of a muscle spindle (stretch receptor) and its afferent nerve fiber. Adrian and Zotterman made use of a small cutaneous muscle of the frog which is supplied by a small twig from the brachial nerve. After cutting away enough of the muscle so that only one spindle remained, it was possible, by use of a vacuum tube amplifier, to record from the brachial trunk the potential changes occurring in the single fiber when the spindle was stimulated by stretching the muscle. It was found that a pull on the muscle generated a succession of regular impulses at a frequency which varied from 20 to 100 per second. Similar observations were made on nerves supplying the sense organs of touch,

pain, and pressure in the skin and on the optic nerve. These observations are quite consistent in showing that when the strength of the stimulus is increased, the frequency of the impulses increases, but there is no change in the size of the action potentials. This is illustrated in Fig. 36, a record of the spike potentials which appear in a leg nerve of a frog when a toe muscle containing only one spindle is stretched. It will be noted that the impulses are uniform in size, although their frequency increases to a maximum as the muscle is extended and then declines as the pull is maintained. It is clear how a nerve fiber which can conduct only in an all-or-none manner can give rise to varying degrees of sensation, for a strong stimulus will cause impulses to be set up more frequently than will a weak one. A strong stimulus will also excite a larger number of receptors.

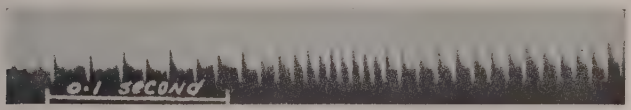

Fig. 36.—Impulses in a single nerve fiber from a frog's muscle spindle stimulated by stretching the muscle. Matthew's toe muscle preparation. The potential waves are all alike; their frequency increases with the tension and then declines slowly when the tension is constant. (From Adrian: *The Mechanism of Nervous Action,* Philadelphia, 1932, Univ. Pennsylvania Press.)

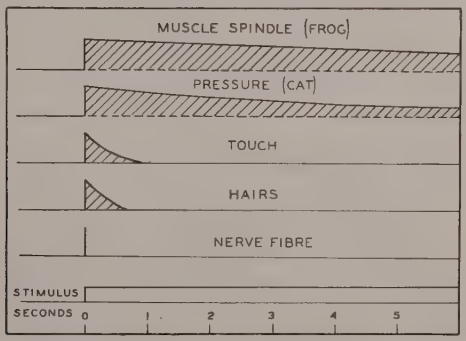

Fig. 37.—Diagram showing the response to a continued stimulus in nerve fiber and different types of receptors. Adaptation is most rapid in the nerve fiber and slowest in the muscle spindle. (From Adrian: *The Basis of Sensation,* New York, 1928, W. W. Norton & Co.)

It can be concluded, therefore, that variations in the intensity of a stimulus applied to any one class of receptors produce variations in intensity of sensation or reflex activity through changes in the number of afferent impulses which reach the central nervous system per unit time.

Discharges in sensory fibers give us our most direct information of the functional nature of receptor organs. The time course of the discharge from different receptors varies considerably. Although frequency of impulse initiation varies with the strength of the stimulus, it always falls off as the stimulus is maintained at a constant intensity. This effect appears in Fig. 36. It represents a phenomenon found in all excitable tissues, namely, the rapid failure of a constant stimulus to excite. A nerve fiber responds to an electric current only when there is a change in intensity above a certain minimal rate—continued passage

of a constant current does not excite. This characteristic, which is called *adaptation,* is most highly developed in nerve, but it is found in all sense organs. Indeed, it forms the basis for an important distinction between receptors of two general types. The first is exemplified by the slowly adapting frog's muscle spindle which responds to a steady pull by producing a discharge of impulses which falls off very gradually during the continuance of the stretch. At the other extreme are the touch receptors and those sensory cells which are excited by bending a hair; a burst of impulses occurs as the stimulus is applied, but this dies out rapidly as the touch is maintained or the hair kept in a final position. Pressure receptors occupy a midposition as regards rate of adaptation. These differences are summarized in Fig. 37. We shall see that reflexes may be broadly divided into those producing sustained postures and those evoking rapid phasic movements. One basis for this distinction can be discerned in the behavior of the different receptors whose stimulation evokes the two sorts of reflex effects. The sustained contractions characteristic of postural activity are typically the result of continued excitation of slowly adapting receptors (muscle and tendon sense organs), while phasic reflexes in which a persistent afferent discharge is unnecessary are responses to sudden changes in the environment which affect rapidly adapting receptors. This difference in rate of adaptation of the two types of sense organs is also reflected in our sensory experiences. We are continually aware of a steadily flexed elbow no matter how long we keep it flexed, but we do not continue to be keenly conscious of wearing a hat, unless we move it about and thus reexcite the rapidly adapting receptors for touch and hair position.

THE QUALITY OF SENSATION AND ITS LOCAL SIGN

Whatever the form of stimulus which excites a given receptor, the quality of the sensation is always the same. A temperature of 45° C. produces a sensation, not of warmth, but of cold when applied to a receptor for cold, and of pain when applied to a pain receptor. Pressure applied to the eyeball gives similarly a sensation of light. This is because, in general, the quality of a sensation depends on the part of the brain to which the nerve impulses set up by the stimulus are conducted. All the fibers from a given type of receptor group themselves together in the spinal cord or brain stem and lead to a common group of cells, or sensory area, in the brain from which the sensation arises. The impulses traveling over these fiber groups are apparently the same in quality no matter what form of physical or chemical disturbance has set them up. Consequently on reaching the brain centers, no difference can be recognized between them, and they all give rise to a common quality of sensation. Two important factors upon which the quality of a sensation depends are: (1) the low threshold of a special group of sense organs for the particular stimulus; and (2) the anatomical arrangement by which the impulses from such a group are conducted to a common region in the brain. From whatever source impulses reach this region the character of the sensation will be the same. These considerations give rise to *the law of the specific properties of nerve,* which is to the effect that, however excited, each nerve of special sense gives rise to its own peculiar sensation.

It is perhaps an undecided question whether differences in anatomical arrangement form the sole basis of differences in the quality of sensations.[99] While the intensity of any one kind of sensation certainly depends on the number of impulses reaching the central nervous system over one group of sensory fibers per unit time, it is possible that different qualities of sensation depend on specific differences in the character of the impulses arriving over different sensory fiber groups. In a study of single impulses from skin and muscle receptors of the frog Matthews[105] found that he could determine the origin of the impulses by the form of the action potential. In fibers connected with cutaneous sense organs of various types the wave was smaller, developed more slowly, and lasted longer than the potential in the muscle sensory fibers. Such differences in the impulses from different receptors might produce distinctive effects on the central nervous system. On the other hand, fiber connections do exist and there is no reason to suppose that each link in the neuron chain leading from sense organ to brain carries impulses of precisely the same velocity and time relations. At the first link in the chain, however, a sensory fiber makes synaptic connections with a multitude of neurons. At this point it may be that the impulse characteristics determine which of several alternate central connections will be activated.

The sensations which are set up by the stimulation of receptors not only have a definite quality, but are recognized as coming from a definite region of space. They are said to have a *local sign*. Certain sensations are referred to parts of our body, as we recognize when we say our feet are cold, our tooth aches, or our skin itches. Others are referred to objects recognized to be in contact with the body, as when we assert that a bed is hard, or a piece of ice cold. Still others are referred to distant objects, as when we recognize the color of a picture, the sound of a bell, or the odor of a flower. In all these cases the process of excitation is located actually in a sense organ within or at the surface of the body, and the phenomenon of sensation is set up somewhere within the brain. The reference of sensation is a psychological phenomenon depending on the past experience of the individual. We have learned, for example, that whenever impulses arrive in certain regions of the brain, giving rise to characteristic sensations, they have come from stimuli set up in some particular group of receptors located in some particular part of the body and excited by a disturbance which we have discovered can come only from some particular region in space. Thus experience tells us that a certain sensation is associated with an object in contact with the foot. Whenever the afferent paths from the foot are brought into play, the same sensation results, and we learn to associate the resulting sensation with the foot and refer all such sensations with accuracy to the foot. If the sensation is one commonly associated only with the obvious contact of some object with the foot, i.e., if it results from a combination of the sense of touch and sensations of other quality, the sensation as a whole is referred to the external object, and we speak of the object being cold, hard, etc. When components of such a sensation occur without the obvious contact of some object, the sensation is referred to the part of the body in which the stimulation arises, and we speak of the foot being cold or in pain. Similarly we have learned to associate sensations resulting from stimuli arising in certain sense organs with objects at a distance from the body. We have learned, for example, to associate sensations which arise from stimuli falling upon particular parts of the retina with the particular regions in space from which light may come which can stimulate that particular retinal area. Unconscious of the mechanism of the optical system, or of the arrangement of the afferent paths of vision, we have simply learned that certain visual sensations can always be attributed to objects occupying a certain position in space, and we

can consequently assert with assurance that the upper part of a picture is blue. The local sign of sensation is consequently largely a matter of experience or learning.

Reflex acts also bear an accurate local sign, although they may be carried out by parts of the nervous system apparently devoid of consciousness or of the ability to learn. Thus a frog, from which the brain has been removed will raise its hind leg and attempt to sweep away an irritating object placed on any part of the body, directing its foot to the point of stimulation with the utmost accuracy. A spinal dog will carry out a scratch reflex which differs considerably in its objective point, depending on the part of the back to which the stimulus is applied. How the mechanism has come about which enables stimulation of receptors in one part of the body to bring about these reflex movements of an appropriate sort is a fundamental problem in evolution which we cannot take up.

The basis of the recognition of quality and local sign in sensation is of the utmost importance in interpreting the sensory manifestation of disease in the central nervous system. It rests on the fact that sensation of definite quality and local sign depends on the arrival at a certain station in the brain of impulses which are set up ordinarily in a group of sense organs specialized for the reception of one particular type of stimulus and located in a definite region of the body. Loss of sensation may result from the interruption of the path of conduction anywhere between, and including, the receptor and the sensory center in the brain.

Sensations of definite quality may be set up by stimulation of the nerve fibers at any point along this path, or of the sensory center itself. One must exercise great care before accepting the location to which the patient attributes the source of sensation, for he has only the experience of healthy life to guide him. Consequently, he may be misguided into ascribing sensations to definite parts of the body, which, in fact, are hallucinations arising from some functional disorder of the brain which is affecting directly the sensory centers of the cortex.

Referred Pain.—The accuracy of sensory location seems to be correlated with the abundance of sense organs in different parts of the body and with the frequency of their employment. On the hands, the lips, and tongue, localization is extremely accurate, for these organs are in frequent use in examining the nature and position of various objects. Localization is good on the soles of the feet, which are used to sound out the ground in walking. On the other parts of the limbs, the trunk, and particularly the back, stimuli can be localized only in a rather rough way. Particularly interesting are the phenomena of localization of sensations arising from the viscera. In healthy life these organs do not give rise to sensory manifestations, but in disease of the viscera acute pains may be set up. Because visceral sensations arise from organs within our body, we have no way of knowing just where the trouble lies and consequently have no basis for localizing the disturbance accurately. In the case of stationary organs, such as the heart, the pain may be referred at times to the proper internal region, but in the case of movable organs, such as the intestine, the reference is most inexact. Very commonly pain arising in the internal organs is referred to some remote region on the surface of the body. This phenomenon is known as *referred pain*. Such pains are sharp or aching in character, whereas pain which seems to come from the internal organs is dull or heavy (Head[102]).

The afferent nerves from the viscera apparently terminate in the cord in close association with afferent nerves from certain skin areas. Just how one group of afferents affects the other is not known, but the fact is that the sensation from the viscus is referred to the peripheral distribution of those fibers which terminate in the same segment of the spinal cord. The nerves of cutaneous sensation have a definite segmental distribution, and consequently the reference of internal pain will be to one or another of these segmental regions. Not only is the visceral pain referred to these segmental areas, but these parts of the skin become hypersensitive, so that the sensation of pain and sometimes of heat and cold arising from them is greatly exaggerated. Thus the location of the referred pain and of hypersensitivity may be taken as an accurate indication of the internal situation of the source of irritation.

All sorts of theories have been offered in explanation of the phenomenon of referred pain. A brief résumé of these has recently been given by Pollock and Davis.[104] One view

is that afferent impulses from a viscus, on entering the spinal cord, lower the threshold to impulses from the skin with the result that the latter continue to the brain in sufficient numbers to arouse a sensation. Standing in support of this or a similar hypothesis is the fact, first brought forward by Lemaire and later abundantly demonstrated by Weiss and Davis,[106] that local anesthetization of the skin area to which a visceral pain is referred relieves the pain. Pollock and Davis consider that visceral stimulation sets up a reflex discharge of impulses in the sympathetic pathway to the skin and that this, through vasomotor or humoral means, excites the cutaneous endings of the ordinary afferent fibers of the cerebrospinal system.

CUTANEOUS AND DEEP SENSIBILITY

The physiology of receptors may be illustrated by a consideration of sense organs which have a general distribution throughout the body. These comprise the receptors of chief interest in practical neurology, and will serve to illustrate principles which apply as well to the special sense organs of the head (of the eye, ear, gustatory, and olfactory epithelia), consideration of which will be found

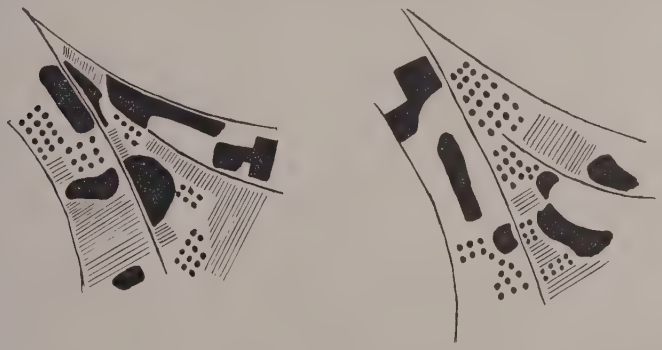

Fig. 38.—Cold spots (*A*) and heat spots (*B*) of an area of skin of the right hand. In each case the most intense sensations were experienced in the black areas, less intense in the lined, and least in the dotted. The blank areas represent parts where no special sensation of either kind was experienced. (From Goldscheider.)

in Part II. They may be divided into organs of *cutaneous* and of *deep sensibility*, depending on whether the receptors lie in the skin or in the internal parts of the body. We can recognize four primary qualities in the sensations to which they give rise. These are touch, heat, cold, and pain. When an area of skin is examined carefully it is found that these sensations are not elicited with equal readiness from all parts, but that definite spots exist which may give rise to one or another of these sensations. Some give rise to touch alone, others to the sensation of warmth, others to that of cold, and still others to a feeling of pain. Each spot evidently marks the location of one or more receptors for the stimulus in question. The spots giving rise to the four different qualities of sensation frequently do not coincide, nor do their numbers correspond, i.e., cold spots are more numerous than heat spots. In many regions of the body one quality of sensation may be lacking altogether. Thus pain is absent from the inner surface of the cheek opposite the second molar; it alone occurs on the cornea. These

facts furnish proof that the quality of the cutaneous sensations depends on the stimulation of sense organs which are specialized each for a different type of stimulus.

Touch.—Touch spots are stimulated by pressure which deforms the tissue. This may be seen to be so by dipping a finger into mercury, when it will be found that the sensation arises only from a band of skin at the surface which is bent by the pressure of the mercury. The skin deeper down is pressed upon uniformly and consequently is not deformed and no sensation is set up. Touch spots are not uniformly distributed on all parts of the body, as we have already indicated. On the hairy regions it is found that they are most numerous at the base of the hairs, especially on the "windward" side. These spots are stimulated when the hair is bent, and since the hair acts as a lever, very light pressures will excite them. Consequently the threshold for touch is lowered on the hairy parts of the body.

The examination of the sense of touch in the skin is important in the study of nervous disease. The presence or absence of the sensation is tested by touching the skin with a pledget of cotton or a soft paintbrush. If the sensation is impaired but not destroyed, more exact information can be obtained by measuring the *threshold,* i.e., the smallest pressure which will stimulate the touch spots by repeating the test with a series of hairs or brushes of graded stiffness. The ability to localize the spot touched is known as *spot finding* or *one dimensional localization.* Two dimensional localization is the process of recognizing that stimulation is being applied to two spots at the same time. If the points of a pair of compasses are applied to the skin at once, they will be recognized as distinct points only if separated by a certain distance. This distance becomes greater as the number of touch spots becomes fewer; it is apparently necessary that a certain number of unstimulated spots should separate them before the points of stimulation are recognized as distinct. This process of recognizing the distinctness of two spots is called *two dimensional localization.* The compass test is useful in detecting deficiencies in the process which may result from destruction of the afferent paths for the sense of touch.

Very closely associated with the sense of touch are the sense organs, which give us knowledge of the position and movements of the parts of our body. These are located in the muscles, tendons, and joints, and are doubtless stimulated by deforming pressures arising from the contraction of muscle and the movement of the bones at the joints. The senses are tested by the ability of a patient to touch one part of the body with another, the eyes being shut and the affected member being moved into various positions. Quantitative measurements can also be obtained by determining through how many degrees a joint may be bent before the patient recognizes that the limb is being moved. The ability to recognize the position and movement of the parts of the body is called *three dimensional localization.*

Heat and Cold.—The heat and cold spots are stimulated by abnormal temperatures, heat spots being excited by temperatures above and cold by temperatures below that previously existing in the skin. Whether one or the other sensation will be felt depends not so much on the absolute temperature to which the heat and cold spots are brought as to the relation of this temperature to that of

the skin. If the skin is chilled, lukewarm water will feel warm to it, whereas the same water will feel cool if the skin has previously been brought to a high temperature. Thus if one finger is placed in cold water and the other in hot water for a few minutes and then both are thrust into water at an intermediate temperature, the sensation of warmth will be felt in the former finger and of cold in the latter. These sense organs thus become adapted to the conditions to which they are exposed, and become excited again only by a change in these conditions.

Pain.—This sensation arises from stimulation of spots which are so numerous and widely distributed that it is difficult to map them with any accuracy. Unlike the other receptors, the pain spots are not specialized for the detection of any particular form of stimulus, but may become excited by any condition which threatens to harm the tissues. Pain may be produced by excessive pressure, the caustic action of chemicals, temperatures above 45° C., and the effects of extreme cold. The threshold for these stimuli is high, so that in the strengths at which they are ordinarily experienced the sensation of pain does not arise. All stimuli of sufficient intensity to threaten the welfare of the tissues and give rise to pain are called *noxious* or *nociceptive*. They characteristically evoke reflex movements which are protective or defensive. That specific sense organs or nerve terminals for pain exist can scarcely be doubted. This is shown by the presence of pain spots in regions from which other sense organs are absent, such as the cornea; by the absence of pain in regions in which other sense organs occur, such as the inside of the cheek opposite the second molar; and by the fact that certain drugs, such as cocaine, may abolish pain without disturbing the reception of other sensations.

ANALYSIS OF SENSATION IN TERMS OF AFFERENT NERVE FIBERS

We have seen on the one hand that certain fundamental modalities of sensation are associated with specific receptor organs and on the other that the cerebral distribution of incoming impulses is an important factor in determining the quality of a sensation. Between receptors and central nervous system sensory messages are carried by fibers of widely different morphological and physiological types. A question obviously raised by this fact is whether different sensations are mediated by fibers of specifically different types. Only a partial answer is available.

Mammalian sensory fibers (those of the dorsal roots) embrace (1) fibers of the large A group with diameters from 20 μ to 1 μ and velocities from 100 to 5 meters or less per second, and (2) unmyelinated fibers belonging to the C group (conduction velocities less than 2 m. p. s.). The sensory fibers once classified as belonging to the B group are now considered to be small A fibers; B fibers are by definition limited to small myelinated motor fibers found in the autonomic system.[47, 60]

A great deal of attention has been devoted to fibers which are concerned in provoking pain. The idea has often been expressed that excessive stimulation of any receptor may cause pain. In terms of modern knowledge of receptor function this would mean that pain is felt whenever there is a high frequency of discharge. It is possible that this may be the case in certain fibers. That

it is not so in the case of certain touch receptors was demonstrated by experiments (Cattell and Hoagland) in which the rapid adaptation of these sense organs was overcome by applying a fluctuating stimulus to the skin of a frog by means of an interrupted air jet and to a hair of a mammal by a vibrating rod.[99] Normal animals to which these stimuli were applied showed not the slightest sign of pain, although it was found that impulses were set up at frequencies of 250 to 300 a second, which are maximal for the fibers in question. Evidence that pain and touch are mediated by different fibers is also afforded by the fact that the area supplied with pain endings by a particular nerve is usually larger than that supplied with tactile endings. Further, there is the fact that when analgesia results from a peripheral nerve lesion which spares other forms of sensation, no amount of stimulation of any kind will evoke pain. Finally, it seems fairly well established that within the central nervous system pain impulses are conveyed by specific fibers.[102] Thus disease of the spinal cord may result in loss of the sensation of pain over a given area without any impairment of touch and deep pressure.

Evidence which suggests some slight modification of the view that pain fibers and pain endings are strictly specific has been obtained by Heinbecker, Bishop and O'Leary (see Heinbecker and Bishop[103]). It was found that when cutaneous pain spots are stimulated by weak single electric shocks a sensation of contact (touch) is produced. (It is to be noted that pure tactile receptors are stimulated mechanically at a lower threshold than are pain endings, but the latter have a lower threshold for electric stimulation.) When the shock applied to a pain spot or to a cutaneous nerve is increased, the sensation grades through nonpainful pricking touch into a definitely painful sensation. The difference between the sensations of contact and prick must in this case be due to the number of successive impulses set up in the individual nerve fibers. The conclusion drawn from these results is that "the threshold sensation induced by activation of the potential pain mechanism is not dolorous, but rather a tactile or contact sense, but the pathways are specific to the extent that only certain pathways and not all pathways for contact sense, are capable of conveying impulses resulting in pain."

Although the bulk of evidence favors the view that pain is always due to impulses in specific fibers, these fibers do not appear to belong to any one group as regards size and functional characteristics. Ranson has demonstrated small unmyelinated fibers in the dorsal spinal roots and given evidence that stimulation of these fibers in animals produces effects which are associated with pain. In accord with this is the finding by Erlanger and Gasser that the slowest and smallest fibers, those belonging to the C group, cause the most pronounced reflex effects. Further, Adrian discovered that various forms of harmful stimulation of the frog's skin characteristically set up slow afferent impulses which may persist for several hours at a low frequency. These impulses do not result from other forms of cutaneous stimulation. When, for example, a gradually increasing pressure is applied, large, rapidly conducted potential waves first appear in the cutaneous nerve, and these are joined, as the pressure becomes greater, by small waves which travel slowly at rates varying from 0.5 to 5.0 meters a second. In their experiments on stimulation of cutaneous nerves in man Heinbecker, Bishop and O'Leary found that pain results when myelinated fibers approxi-

mately 6 to 3 microns in diameter and conducting at rates of 30 to 15 or less meters a second are stimulated. These were thought at the time to belong to the B group, but on the basis of the present classification (see page 49) we must regard them as among the medium and slow A fibers. These investigators also confirmed the fact that the unmyelinated fiber group contains pain fibers. Further evidence that pain is mediated by fibers of the A group is presented below.

There are two effective means of differentially blocking nerves. One of these is the common surgical practice of surrounding a nerve by cocaine or one of its substitutes (procaine or novocaine is most widely used). When this is done in a conscious human being, it is found that sensations disappear in a fairly definite order. There is general agreement that pressure sense is most resistant to local narcosis, and that cold is blocked before warmth. There is some disagreement in connection with the relative positions of pain and temperature. According to the most recent work (Endres; Heinbecker, Bishop, and O'Leary) the order of disappearance is: cold, warmth, pain, pressure. Gasser and Erlanger showed that when cocaine is applied to a segment of isolated nerve, first the C and B waves and then in turn the various subdivisions of the A wave disappear. Therefore cocaine blocks conduction in small fibers first. The differentiation, however, is not exact; some fibers in a faster group are always blocked before all the fibers in the immediately preceding slower group. The most certain conclusion to be drawn from these experiments is that pressure fibers include the largest axons in a nerve. Further conclusions may be drawn after we have considered the results of another mode of investigation.

The application of pressure is a second method of securing a differential block of nerve trunks. This may be done in human beings or animals by inflating a sphygmomanometer cuff placed around a limb. In animals it may be accomplished by applying pressure to a segment of nerve placed in the chamber designed by Gasser and Erlanger. In any case it appears that the blocking is the result of local asphyxia from ischemia[101] (compression of an *isolated* nerve blocks fibers, but in a different order). The various investigators who have studied block by pressure in human subjects are agreed that the several kinds of sensation drop out in the order: pressure, cold, warmth, pain. Differentiation is good between pressure and cold, on the one hand, and warmth and pain, on the other. But separation between pressure and cold is difficult and it is thought that pain cannot be separated from warmth at all.[101] Clark, Hughes and Gasser[100] have studied the order in which the different fibers of the saphenous nerve of the cat are blocked when a sphygmomanometer cuff on the leg of the animal is inflated. The order of disappearance was found to be the same in all preparations. The B elevation of the compound action potential disappears first.[60, 100] When the B fibers have ceased conducting, a large fraction of the A elevation is still present. Within the A group the faster components are more vulnerable than the slower. The C elevation remains almost entirely intact at a time when the A and B elevations are completely eliminated. Under these conditions circulatory and respiratory reflexes characteristic of pain can be produced (barbiturate anesthesia). When the time relations between the disappearance of sensation in man and the disappearance of the elevations of the potential in the cat are compared, a close parallelism is found. After an initial period of fifteen minutes during which little change occurs in either experiment, the impairment of pressure and cold in man occurs at the same time that the A and B fibers in

the cat fail to conduct. After forty-five minutes of block only C fibers are conducting in the cat, and pain and warmth are the only sensations remaining in man.

A comparison of the order in which sensations and the elevations of the electroneurogram are affected by cocaine and by compression (asphyxia) gives a fair idea of the distribution of the different modalities of sensation among the fibers of a nerve trunk. Such a comparison has been made by Gasser,[101] and his conclusions may be briefly summarized. Pressure is the last sense to yield to cocainization, but it is not blocked by asphyxia until a time when the A elevation would be extinguished. It must therefore be mediated by fibers widely distributed through the A group. Since cold is not felt when only C fibers should be functioning, and is present when B fibers should be blocked, it appears to be distributed among the A fibers. The results with cocaine, however, show that the largest fibers concerned in producing this sensation are smaller than the largest fibers mediating any other sensation. Its position, which appears to be the most restricted of all, is probably among the smallest A fibers. The comparison confirms the evidence, already mentioned, that pain must be mediated by fibers with very different positions in the velocity range. The cocaine experiments indicate that the largest pain fibers are second in size only to pressure fibers. The compression experiments show that pain is still conducted when the A and B elevations have disappeared; they augment the considerable body of evidence that pain is mediated by C fibers. Warmth is also mediated by a rather wide range of fibers. The cocaine experiments show that the largest warmth fibers are larger than the largest cold fibers, while the inseparability of warmth and pain under the influence of asphyxia indicates that warmth may be carried by C fibers. Such are the general conclusions to be drawn from this particular mode of investigation. Gasser insists that the formulation is one which should be regarded as tentative, and suggests that it will be subject to numerous revisions.

Pure sensations, arising from the stimulation of a single type of receptor, rarely occur in life except under the artificial conditions which we employ in the laboratory. The sensations which we experience are the composite results of the simultaneous combination of a variety of stimuli, acting together on sense organs which give rise to sensations of different quality. The nature of the resulting sensation is consequently modified. Water heated to 40° C. feels warm to the hand and stimulates only the heat spots. At 45° C. the cold spots and pain spots are also excited, and the resulting sensation takes on a distinctly different quality which we call "hot." Since pain is excited only by extreme intensities of stimuli which can also set up other qualities of sensation, it is natural to find painful sensations varying considerably in their quality, depending on the sensations which occur in association with them. Thus a throbbing pain is due to the simultaneous pressure produced by dilated blood vessels.

It is interesting to find that certain qualities of sensation are incompatible with one another. When stimuli capable of setting up two such incompatible sensations occur at once, one sensation is suppressed or inhibited by the other. An interesting experiment is described by Head which illustrates this. The tip of the glans penis is supplied with receptors for cold and pain, but may be devoid of heat spots. If it is dipped into water at 40° C. the pain spots alone are stimulated and a disagreeable, painful sensation results. If the temperature is raised to 45° C. the cold spots also are stimulated, the pain is displaced by a vivid sensation of cold. About the corona of the penis heat spots also occur. If this region is also immersed, the quality of the sensation changes to one of exquisitely pleasant warmth. If the water employed in the experiment is at a temperature higher than 45° C. the painful sensation persists and no sensation of warmth is felt. The sensations of pain and pleasant

warmth are incompatible and cannot occur simultaneously. Which one will succeed in gaining control of consciousness and in suppressing the other depends on the relative strengths of their stimuli. An entirely analogous phenomenon occurs in the competition of incompatible reflexes for the control of a common motor path (page 127).

Noxious stimuli give rise to an exceedingly impelling sensation and to reflexes which can dominate over any others which may be set up at the same time. The response to painful stimulation is of a protective character and it is imperative that such stimuli and their sensations should control the activity of the organism when they arise with intensity. On the other hand, if the noxious stimuli are near the threshold value of intensity, and little danger is threatened, it is an advantage that its effects be suppressed so that the organism may react with a discretion based on data derived from other sensations as well.

CHAPTER X

DISCHARGES IN MOTOR NEURONS

The problem of behavior is essentially the problem of explaining how the central nervous system distributes messages to muscles in such quantities and with such dispersion in time and space as to bring about the sequence of integrated motor events which compose any normal body movement. This general problem must be attacked on each of its many sides by a variety of methods and we cannot hope to derive great insight from any single one. In Chapter IX some attention was devoted to the nerve impulses which enter the central nervous system to produce sensation and reflex acts. It was related how studies of discharges in afferent nerve fibers have not only given a basis for an understanding of sensation but have also disclosed something of the way in which receptor organs respond to stimulation. If we now turn the process about by examining discharges in efferent nerve fibers, we can scarcely expect to learn much of the nature of the central activity, for the central organ is infinitely more complex than any receptor, but we may in this way obtain information as to how the centers utilize their motor connections in the control of movement.

It is not possible to discover precisely the way in which motor impulses are sent out by studying the muscular contractions they produce. It will be recalled that the unit of neuromuscular response is the motor unit consisting of an individual neuron and the bunch of muscle fibers which it innervates. An increase in the tension developed might be the result of activity in more motor units, or of an increase in the frequency of discharge in the motor fibers already active. We know that motor fibers stimulated electrically conduct in an all-or-none manner, but there remains the rather remote possibility that when these are stimulated normally, they transmit impulses which vary in size with the stimulus. A greater muscular response might therefore be the result of the arrival of impulses of greater magnitude. Because of the tendency of motor units to respond out of phase with one another, the summed action currents led from a nerve trunk or from a whole muscle are likely to be so complex that scarcely more information can be obtained from them than from the contraction itself.

It was not until the responses of individual motor units were recorded that an unequivocal picture of the true nature of the motor discharges was obtained. This was first achieved in 1928 and 1929 by Adrian and Bronk[107, 108] who recorded the impulses in single motor nerve fibers. The technique which made this possible consisted in almost completely dividing the motor nerve so that only three or four fibers remained intact and then examining the responses in the nerve fiber distal to the division by means of the capillary electrometer and valve amplifier. Sometimes it was possible to carry the dissection to a stage at which only one fiber remained connected with the central nervous system. It was found that the single fiber carried impulses varying in frequency over a range from 10 to 90 a second. The size of the individual impulses in any one fiber did not vary under any circumstances. Thus was added a final demonstration that the all-or-none principle holds for normal as well as for artificially induced nerve conduction. Fig. 39 shows the action potential spikes signalling discharges in individual fibers of two different motor nerves.

During normal breathing in the anesthetized rabbit each phrenic fiber carries impulses at a frequency of about 20-30 a second throughout the period

of inspiration. When forcible inspirations are induced by clamping the air tubes to the trachea, the frequency rises to 50-80 a second. There is no change in the size of the action currents when the force of the inspiration is increased or decreased, the only change being in the frequency of the discharge. With low frequencies the different nerve fibers discharge out of phase with one another, but with high frequencies, as in forcible breathing, there is a tendency toward synchronization, and the total discharge in the nerve then consists of volleys from the majority of cells in the phrenic nuclei of the cervical cord. Adrian and Bronk could find very little indication that in the phrenic additional fibers are brought into action when the force of inspiration is increased. The grading of contractions in the diaphragm seems to depend mainly on changes in frequency. As we shall see, this single provision is not of universal occurrence. Indeed in

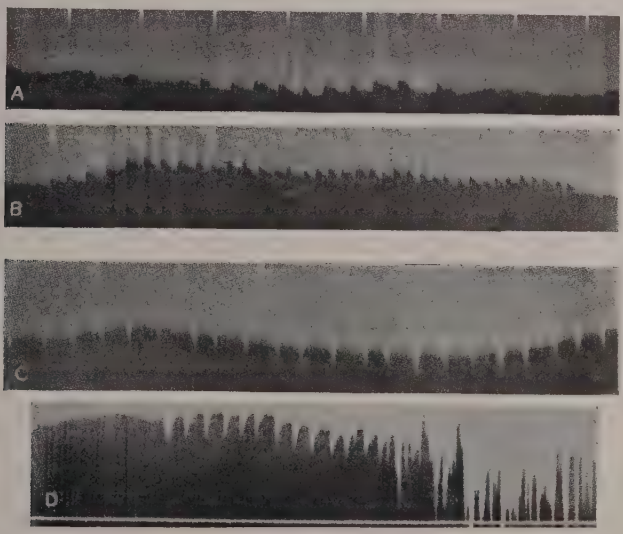

Fig. 39.—Discharges in motor fibers. Capillary electrometer records. Nerves cut down to show activity of individual fibers. *A* and *B* from upper root of phrenic (rabbit). *A*, normal breathing—impulse frequency 28 per second; *B*, forcible inspiration due to clamping air inlet—frequency 50 per second; *C*, nerve to vastus lateralis (decerebrate cat), showing persistent discharge at 25 per second; *D*, the same, beginning of crossed extensor reflex, showing single fiber in action at first, and the entry of more fibers as the contraction develops. Time marker gives intervals of 0.125 sec. (From Adrian: *The Mechanism of Nervous Action.* Univ. Pennsylvania Press.)

the case of the nerves to the intercostal muscles, Bronk and Ferguson found that grading of muscular contraction is due to changes in the number of active fibers as well as to alterations in the frequency of impulse discharge in individual motor fibers (see Fig. 219, page 558). When one considers the phenomenon of summation of contractions, it becomes obvious that variations in frequency of motor nerve discharge between 20 and 80 a second can account for considerable grading in the strength of the contraction of the diaphragm. At low rates of discharge the muscle fibers of each unit will give an incomplete tetanus or even a series of twitches, but since the units are not working in unison the diaphragm as a whole will contract smoothly. When the frequency in each fiber rises to

about 60 a second, a complete tetanus will result, and it will then make no difference, as regards smoothness of contraction, whether the different neurons are discharging in or out of phase. On artificial stimulation of the whole phrenic it is found that an increase in frequency from 25 to 60 a second doubles the suction produced by the descent of the diaphragm.

By this same method it was possible to obtain records of reflex impulse discharges in individual fibers supplying various limb muscles. Two reflexes were studied by Adrian and Bronk: the flexor reflex of the spinal cat and the reflex of crossed extension of the decerebrate cat. Application of a harmful stimulus to the foot of any animal results in its withdrawal; this is the flexor reflex. When elicited by mechanical stimulation of the foot the discharge in an active nerve fiber to a flexor muscle is a series of impulses recurring fairly regularly at a frequency varying from 5 to 45 a second. The frequency increases as the muscle develops tension. Evoked in this way through receptors the reflex con-

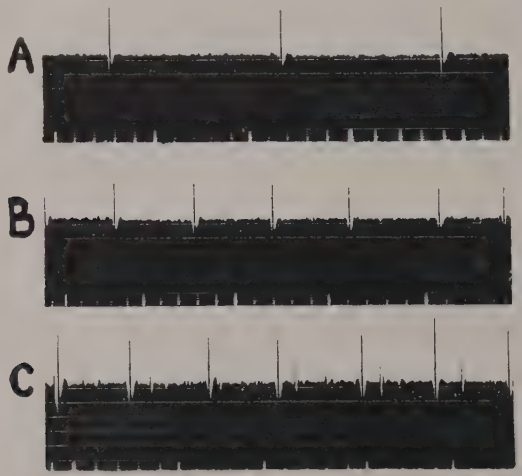

Fig. 40.—Motor unit responses from biceps muscle of a normal human subject during increasing voluntary effort (flexion at elbow). Action potentials recorded by Du Bois oscillograph. *A*, weakest possible effort, frequency 5 to 6 a second; *B*, stronger effort, frequency 9 a second; *C*, still stronger effort, frequency 11 a second and accession of a new unit at 10 a second. (From Lindsley: Am. J. Physiol. 114: 90, 1935.)

traction is graded mainly by a change in frequency, for there is little evidence that a stronger response involves more motor neurons than a weaker one. In the decerebrate carnivore the crossed extensor reflex takes its origin from a background of exaggerated tonus of the extensor muscles. During this condition of postural contraction (decerebrate rigidity) individual extensor nerve fibers show persistent discharges ranging from about 5 to 25 a second. When the crossed extensor reflex is evoked by stimulation of the opposite hind foot, these discharges rise in frequency and may attain rates as high as 90 a second, and there is evidence that many additional motor neurons come into action. From this it is evident that the steady tonic contraction of the extensor muscles is maintained by the asynchronous subtetanic contractions of the fibers of a small fraction of the motor units, while the phasic extension is due to the development

of a complete tetanus in these and many additional units. By an entirely different method Denny-Brown[118] secured results which led to conclusions identical with those of Adrian and Bronk.

It might be supposed that voluntary muscular contractions in man are brought about in a somewhat different way than the reflex contractions of spinal and decerebrate cats. Evidence on this point cannot, of course, be obtained by recording the impulses in single motor nerve fibers. But the nerve fiber discharge is directly reflected in the electrical response of the group of muscle fibers which it innervates. By inserting into a normal human muscle a hypodermic needle arranged in the form of two electrodes of very small dimensions, Adrian and Bronk were able to lead off the action currents arising in a very restricted area of the muscle and so to record the activity of single motor units. Their very definite results have been confirmed and extended by others, especially Lindsley[134] who has made use of special electrodes. No electrical activity is found in any part of a relaxed human muscle. With the initiation of slight voluntary contraction sharply isolated action potentials appear (Fig. 40). During the weakest possible willed contraction the lowest frequency of motor unit response is 3 a second; usually it is 5 to 10 a second. As the contraction becomes more powerful the frequency in the already active units increases and additional units are recruited. The highest frequency found during the strongest possible voluntary effort is 50 a second. Usually it falls within the range of 5 to 30 a second. Lindsley found that the upper frequency limit varies somewhat in different muscles; this may be associated with differences in the rate of stimulation required to produce a complete tetanus (see page 21). We may conclude that voluntary contraction is brought about in quite the same fashion as is the crossed extension reflex of the decerebrate cat, namely, by slow rates of discharge in fewer fibers when the contraction is a weak one, by higher rates of discharge in more nerve fibers when the contraction is a strong one. Change in frequency probably acts to grade contractions delicately while change in the number of units in action is the most effective way of varying the strength of contraction.

It is evident that a relatively weak sustained contraction of any kind in skeletal muscle is the resultant of a series of twitches or incomplete tetani in a certain fraction of the muscle fiber groups. The asynchronism of this intermittent activity permits the muscle as a whole to exert a steady pull. We have seen that muscular contraction of this type is uneconomical, that it requires a greater expenditure of energy than one due to complete tetanus in fewer fibers. But it probably has one great advantage in that intermittent contractions have the mechanical effect of speeding up the flow of blood through a muscle. This would tend to prevent the accumulation of metabolites and to postpone the development of fatigue. A possible rotation of activity among motor units has been invoked to explain the maintenance of sustained postural contractions without fatigue. Experiment shows, however, that a series of twitches or even incomplete tetani can be kept up almost indefinitely without fatigue in a mammalian muscle with blood supply intact. There is therefore no *a priori* reason for rotation. As a matter of fact neither Adrian and Bronk, Denny-Brown nor Lindsley could find any indication of rotation in the single unit rhythm when the extensor muscles were exhibiting a high degree of sustained postural contraction. Similarly in smooth, moderate, sustained voluntary contraction the individual unit maintains its slow rhythm without cessation for as long as thirty minutes, and there is no evidence of rotation of activity, or substitution of units (Lindsley[134]).

CHAPTER XI

THE ORGANIZATION OF THE MAMMALIAN CENTRAL NERVOUS SYSTEM: FUNCTIONAL LEVELS

The organization and activities of the central nervous system are so complex that it will be necessary in the chapters which follow to treat each aspect separately and with little reference to its relation to the organization of the whole. Artificial as such a presentation may seem in describing the organ of integration, it is, in fact, a counterpart of the only effective experimental procedure by which the central nervous system can be studied. In neurophysiology analysis must proceed, as it must in all experimental science, by first simplifying the experimental conditions. Little of the fundamental working of the system is revealed to the mere observer of its complex motor achievements. It is necessary to restrict the field of total possible action. This can be done either by surgical ablation and separation of parts or by limiting the conditions of stimulation so that only a fraction of the nervous system responds to any appreciable extent.

The early phylogenetic development of the nervous system led to a central organ arranged in segments. In the lower worms each segmental ganglion exhibits a high degree of autonomy, so that most of its segmental activities are undisturbed by separating it from adjacent ganglia. The process of cephalization, which took place as the invertebrates developed and which occurred in an even more striking manner during vertebrate evolution, resulted in an ever increasing dependence of the aboral segments on the head ganglion or brain. Indeed there has gone hand in hand with increase in size and complexity of the brain a tendency of this organ to take over, elaborate, and control functions which in lower forms are governed almost entirely by the individual segments. But even the spinal segments of man retain, as we shall observe, some small portion of the primitive autonomy, and when the spinal cord of a carnivore is completely separated from the brain it remains capable of mediating simple items of behavior which are but slightly removed in character from similar movements evocable in the intact animal. When the lower parts of the brain stem are left connected with the cord, more complex activity is possible. If only the cerebral cortex, that most recent and most complex product of cephalization, is removed in a cat or dog, the behavior deficit is even less. In other words, the central nervous system is roughly organized on the basis of what may be termed "levels of function."

The brain has developed in connection with, and perhaps partly because of, an immense concentration of special sense cells at the headward end of the body. No better statement of this fact and its consequences could be given than the following taken from a lecture by Sir Charles Sherrington.* "That leading end, the head, has receiving stations signalling from things at a distance, things which the animal in its forward movement will next meet. A shell of its immediate future surrounds the animal's head. The nerve-nets in the head are

*_The Brain and Its Mechanism_, The Rede Lecture delivered December 5, 1933, Cambridge University Press, 1933.

therefore busy with signals from a shell of the outside world which the animal is about to enter and experience. The brain has thus arisen where signalling is busiest and is fraught most with the germ of futurity. Small wonder then that the brain plays a great role in the motor management of the muscle. Nerve management of muscle resolves itself largely into management of nerve by nerve, especially by brain, more and more so as evolution proceeds. With no greater equipment of muscle the superimposed amount of nerve becomes greater and greater; each new nerve-growth seems to entail further nerve-growth. Fresh organization roofs over prior organization. Brain is an example. 'So on our heels a fresh perfection treads.' But were it a government office we might be suspicious. This brain of ours is a perfect excrescence although our endowment in muscle remains but moderate."

As the central organs of the distance receptors, the more highly developed brains add substantially to the number of activities presided over by the nervous system. With this addition reorganization of the older system has of necessity occurred. This was first pointed out clearly in 1884 by the British neurologist, Hughlings Jackson, when he made the suggestion that the nervous system is organized in such a way that the primitive reactions of the older parts are prevented from dominating behavior by inhibitory influences emanating from the higher levels. On this view we may suppose that the latter hold in check those activities of the lower, more archaic levels, which would seriously interfere with their more discriminative reactions. The principle which Jackson formulated has greatly influenced modern studies of the nervous system, and its essential correctness is supported by a wealth of physiological and clinical evidence. We may expect therefore that removal of some rostral part of the cerebrospinal axis, either by disease or the operative procedures of physiologist or surgeon, will result in changes which can be classified in two distinct groups as *deficiency phenomena* and *release phenomena*. When a lower level of organization is separated from a superior level, we observe against a background of functional loss not only the independent activities which this level carries on in the normal animal, but certain additional or excessive activities commonly held in check by the higher centers. Thus we shall see in the decorticate and decerebrate animal that removal of the control of the highest level allows the sustained contraction of posture to become greatly exaggerated in the extensor muscles. The so-called spastic paralysis which accompanies many cerebral and spinal lesions in man is in all probability a similar release phenomenon.

A brief review of the capacities and abnormalities of different animals in the spinal, decerebrate (bulbospinal), and decorticate states will reveal much of the different functional levels. The indissoluble union of structure and function is nowhere so obvious as in the organization of the central nervous system. A perusal of the remainder of this part of the book will demand a good working knowledge of human and mammalian neuro-anatomy. Space does not permit a treatment of this complex subject and the reader is referred to the many available sources of information.

THE SPINAL ANIMAL

Spinal Shock and the Recovery of Spinal Reflexes.—In animals the spinal cord may be separated from the brain by transection at one of the upper cervical segments. If the mammalian preparation is to be kept for more than a few

hours, the level of section must be below the fifth cervical segment, thus leaving the phrenic roots connected with the bulbar respiratory center so that diaphragmatic breathing may continue. Higher cervical section necessitates, of course, artificial respiration and in laboratory animals this cannot be maintained readily for any great period of time.

Immediately after the operation a condition of depression sets in, involving many or even the majority of reflex arcs in the separated segments of the cord. This condition is known as *spinal shock*. It supervenes in all classes of vertebrates, but is much more profound and longer lasting in the higher than in the lower members of the group. For example, in the frog it passes off in a very few minutes after which complicated purposive limb movements can be evoked, and nearly normal postures can be assumed. In the spinal dog or cat, on which a great deal of work has been done, the involved regions of the body are temporarily profoundly paralyzed in respect to certain reflexes. In the monkey all reflexes may be inelicitable for several days. In all animals inability to maintain a normal body temperature in the face of even slight changes in environmental temperature is a permanent deficit (see Chapter LIX); the irreversible loss of capacity to change the position of the body as a whole favors the development of pressure ulcers on the skin, and dilatation of cutaneous blood vessels accentuates this difficulty. The arterial pressure is at first greatly depressed and cannot be elevated by reflex stimuli. The bladder fails to empty normally, and accumulation of urine may lead to serious difficulties (see Chapter LXXXIII).

With reasonable attention a cat or dog may survive transection at any level below the fifth cervical segment for many weeks or months. After an interval of a few hours the hind limbs, although completely paralyzed so far as voluntary and other movements of cerebral origin are concerned, begin to show remarkable reflex activity. During the period of spinal shock they are limp and flaccid, but one reflex is elicitable; in fact it is preserved with low threshold and can usually be brought forth in considerable strength immediately after transection.[146] This is the *flexor reflex*. It is elicited by applying any nociceptive stimulus to the skin or deeper parts of a lower extremity, and when fully developed consists in a flexion of the leg at all joints. The evident object of this movement is to remove the stimulated parts from the source of the stimulation, and it is plain that most of the stimuli that produce the reflex are such as would cause in the intact animal a sensation of pain. Intimately associated with the flexor reflex, but more definitely affected by spinal shock, is the *crossed extensor reflex*. After recovery from shock, flexion of one hind leg in response to nociceptive stimulation is invariably accompanied by extension of the opposite or contralateral limb. Thus is revealed a spinal mechanism for supporting the weight which is shifted when one foot is withdrawn from the ground in response to a harmful stimulus. Although it seldom suffers complete extinction during spinal shock, the *knee jerk* is another extensor response that becomes vigorous after the elapse of some time. This reflex is obtained by tapping the tendon which connects the patella with the tibia, the response being a smart contraction of the extensor muscles of the knee joint. The adequate stimulus is a stretch, a form of proprioceptive stimulation, applied to the very muscles which respond. With the return of extensor responses the arterial pressure regains a normal level and pressor reflexes may be obtained by stimuli applied to the region innervated from the isolated cord.

That a nociceptive reflex should not be affected by spinal shock and that its postural accompaniment, the reflex of crossed extension, should be among the first reflexes to recover are facts of considerable interest. They indicate that a primitive protective mechanism is resident in the cord and may operate independently of the higher centers. Experiments by Forbes and Miller and by Leese and Einarson[133] have shown how unnecessary supraspinal levels are for the execution of the flexor reflex. In decerebrate cats they found that when the response is evoked by stimulation of afferent fibers in a leg nerve the discharge over motor fibers is well on its way to the flexor muscles by the time ascending impulses, set up by the stimulus, have reached the brain. In other words, the motor act of flexion is well started before the animal experiences the painful stimulus which calls it forth.

It is comparatively late in the recovery of the animal before reflexes dependent upon stimulation of tactile receptors are shown in any prominent way. The most important of this latter group of more special reflex movements include the so-called scratch reflex and the extensor thrust. The *scratch reflex,* as its name implies, is the scratching movement of flexion and extension of the hind limb at a rate of about four contractions per second that occurs when a mechanical stimulus is applied to the flank and shoulder area of the animal. For example, if we gently draw a pencil or the fingers backward and forward among the hairs on this region of the spinal animal, the corresponding hind limb will be brought up so that the claws are approximately at the place stimulated, and the limb thus directed will undergo a series of flexions and extensions, designed evidently for the purpose of scratching the area of skin that has been stimulated. If the stimulus is a weak one, only the initial stages of the movement may occur, such as the preliminary flexion of the leg. The stimulus calling forth this reflex is very specific in nature. A pin prick or rough friction of the reflex area will not produce it, neither will the application of heat, nor a single electric shock. The most adequate stimulus is one simulating as nearly as possible the condition which would be produced by the movement of some insect on the flank of the animal. This more or less complicated scratch reflex can of course also be elicited in animals whose spinal cord has not been cut, but we cannot predict in such cases whether the reflex will occur. The brain may inhibit the reflex arc and prevent the movement. In a spinal animal, however, the reflex always occurs provided an adequate stimulus is applied. The *extensor thrust* is elicited by applying pressure to the pad of the paw or the sole of the foot. It consists of a quick extension movement of the corresponding limb usually with a flexion of the opposite limb.

After complete recovery from shock, the paralyzed parts of the body are capable of performing even more complex movements than those already mentioned. For example, if the animal is held up with the hind legs hanging down, these will often exhibit rhythmic flexion and extension movements, with the two limbs acting alternately, as they would in walking or running. This is sometimes called the *mark-time reflex.* Another complicated movement may be produced by placing the animal in water, when it may make the movements of swimming, but its swimming will not be sufficient to keep it on the surface. These swimming movements are more perfect in the spinal frog.

After complete recovery from spinal shock a standing posture may be maintained if the limbs are passively placed in the proper position. This spinal

standing is, however, subject to sudden lapses. Occasionally, at a late stage, the extensor muscles may enter a state of rigidity not unlike that which characterizes the decerebrate condition. In female spinal dogs impregnation may occur and pregnancy and lactation may then proceed in normal fashion.

When we pass from the carnivores to a higher mammalian type, namely the monkey, spinal shock is very much more marked and recovery slower. Both flexor and extensor reflexes may be obliterated for several hours or even several days. The knee jerk, which is seldom completely lost in cats and dogs, is almost always inelicitable for at least some hours. In the chimpanzee the hyporeflexia following spinal transection may be as deep as in man (see below). In all primates the first reflex to appear is digital flexion. Flexion at knee or hip always returns later. It is significant that this order of recovery is the reverse of that which is seen after the paralysis which ensues from removal of the motor area of the cerebral cortex.[125]

It is clear that a considerable perfection of execution is possible in acts managed by the isolated cord of one of the lower mammals, although it may be doubted that such acts fully attain the degree of coordination which they exhibit when supraspinal influences are in operation. Their comparative perfection justifies their use in the study of the fundamental properties of the nervous system; their freedom from interference by acts of higher origin makes such a study practical.

The Cause of Spinal Shock.—It would seem natural to suppose that the cause of the depression in reflex activity which follows transection of the spinal cord is the irritation set up directly in the tissues injured by the lesion. This irritation might be thought to have an inhibitory influence of some sort on spinal reflexes, possibly by setting up descending impulses which exert inhibitory effects on the spinal motor neurons. That this supposition is incorrect is shown by the fact that after the shock induced by a cervical transection of the cord has worn off, a second transection at a lower level does not cause its reappearance.

Spinal shock might be thought to be due to the disturbance in the circulation which follows the spinal transection, but this cannot be the case because all parts of the body would suffer alike from the fall in blood pressure, whereas only those parts of the nervous system *below* the lesion exhibit shock. This aboral incidence of shock is a very striking characteristic. So slight is the effect of a spinal transection upon the higher centers that men who have been shot through the spine may not even lose consciousness. They are aware that sensations from the lower limbs have suddenly been cut off, and their first impression is that they have been blown in two. Sherrington has described a monkey, the cord of which was cut below the cervical region, which immediately after the operation amused itself by catching flies with the anterior extremities, whereas the posterior extremities were in a condition of the profoundest shock.

Another hypothesis is that the arcs of the reflexes subject to shock involve conduction to the brain and back again and that depression of the reflex is the result of interruption of the normal central path. Against this supposition may be urged the very brief latencies of the knee jerk in intact animals and man and the fact that in the case of most of these reflexes the motor discharge over ventral roots occurs before any ascending impulses can reach the brain. Positive evidence supports another view, namely, that spinal shock is due to the

cutting off of impulses descending from the brain. It has been shown that the effect of transection just above the pons has precisely the opposite effect from that of spinal transection upon flexor and extensor reflexes. In the decerebrate cat or dog the knee jerk and crossed extensor reflex are exalted while the flexor reflex is less active than in the spinal state. It seems likely therefore that the descending influence whose removal confers upon these reflexes their spinal character has its origin in the region of the medulla oblongata. The experiments of Fulton, Liddell and Rioch[164, 165] have indicated that the vestibulospinal and probably other bulbospinal pathways are mainly responsible for the differences between the decerebrate and spinal knee jerks. It was shown that the ready inhibition which characterizes the knee jerk of the spinal cat (Fig. 51) can be produced in the decerebrate animal by lesions which interrupt this descending system of fibers. Since, as we shall see, decerebrate rigidity is primarily due to overactivity of the vestibulospinal system there is good reason to believe that in carnivores spinal shock is chiefly the result of withdrawal of impulses which, originating at a bulbar level, descend to produce two effects: facilitation of excitation of the motor neurons concerned in extensor reflexes, and inhibition of reflex discharges to flexor muscles.

In the primate (monkey) lesions of the vestibulospinal system fail to produce a depression of reflexes resembling that which ensues upon spinal transection.[124] But here injury in the motor area of the cerebral cortex or interruption of corticospinal (pyramidal) paths results in a temporary condition very similar to spinal shock (Fulton and Keller[288]). A similar depression of reflexes whose arcs are entirely spinal is not a conspicuous result of cortical removal in carnivores and other mammals below the primates. The part played by the cutting off of impulses of cerebral cortical origin in the genesis of spinal shock in primates has been clearly demonstrated by Fulton and McCouch.[125] To comprehend the significance of their results it is necessary to understand that removal of the motor area of one cortex in monkeys, baboons and chimpanzees leads to an immediate paresis of reflex and voluntary movements of the musculature of the opposite side of the body (see page 221); at first the depression is deep and resembles the shock following spinal transection, but considerable recovery occurs, first in the proximal segments of the affected limbs, last in the fingers and toes. The higher the primate the greater is the effect and the slower the recovery. Now Fulton and McCouch found that when spinal transection at a lower thoracic or upper lumbar level was carried out at an appropriate interval after unilateral ablation of one motor area recovery of reflexes occurred in the previously paretic leg earlier than in the previously normal limb. This asymmetry of reflex recovery was found to be proportional to the magnitude of cortical innervation of the cord; thus it was far greater in the chimpanzee than in the monkeys. It is apparent that in animals with greater cerebral development the excitability of spinal reflex arcs depends to a very considerable extent upon descending impulses of cortical origin, whereas in lower mammals it depends chiefly on impulses in bulbospinal or other descending systems of subcortical origin. In this fact we see an example of that forward shift of control which has accompanied cephalization.

It has been pointed out that the depression of such responses as the knee jerk by spinal transection cannot be due to interruption of the central portions of their arcs. The afferent impulses set up by the stimulus enter the cord, traverse a few segments (in some cases only one segment), and stimulate the

appropriate motor neurons. In almost all spinal arcs there are undoubtedly some direct connections between dorsal root fibers and the motor cells of the anterior horn, but conduction also involves internuncial neurons arranged in collateral chains (*M*, Fig. 45) so that any afferent impulse entering the cord over a single fiber sets up impulses over several internuncials and in this way produces multiple stimulation of motor neurons. As we shall see, it requires the impingement of several coincident impulses to excite a motor neuron and the internuncial arrangement is one device for achieving that end. The facts concerning spinal shock show that it is due to deprivation of impulses from the brain and it is therefore of interest to know whether these descending impulses which normally maintain the reflex excitability of the spinal arcs act on the motor neurons directly or exert an effect through the internuncials. By recording the discharges over motor neurons and the activity of cord internuncials (by a method described in the next chapter) McCouch and his associates[150] have been able to show that in dogs and cats spinal transection causes depression only of the internuncials, whereas in monkeys it also produces deep and prolonged depression of the motor neurons.

Spinal Shock and the Recovery of Spinal Reflexes in Man

The potentialities of the spinal cord of man were not fully realized until the World War when investigations by Head and Riddoch[102] on men who had been shot through the spine showed just how complete a recovery can be made from such an injury if the patient is given proper care. In cases of complete transection of the cord there usually results in man, as in the other mammals, a complete loss of reflex activity and of tone in those parts of the body innervated from segments of the cord which lie below the lesion. Occasionally the cremasteric and bulbocavernous reflexes may still be elicited. Below the lesion there is complete anesthesia, the skin is dry and readily becomes gangrenous, and the urine and feces are retained. After a period varying from one to three weeks the first reflexes reappear. These are the flexion reflexes in response to harmful stimuli. At first they can be elicited only from the part of the receptive field which normally is most sensitive, i.e., the sole of the foot, and involve those muscle groups which are normally brought into play by the weakest stimuli. Movements of the toes are consequently the only part of the reflex figure to display itself in the earliest stage of recovery. Later the receptive field becomes more and more extensive and the response spreads to additional groups of muscles until the entire leg is thrown into flexion. As it does so the reciprocal inhibition of the muscles antagonistic to the flexors takes place in a normal manner, just as it does in the spinal cat or dog. Finally, however, a stage of recovery is reached in which a phenomenon occurs which is quite unlike anything seen in these animals. It is called the *mass reflex* and consists in an extensive spasm of the flexor muscles of the abdomen and lower extremities which is brought about by harmful stimuli applied almost anywhere to the parts of the body affected by the injury. Accompanying the response there is a pronounced outburst of sweating in the affected regions and if the bladder is as much as half full, a reflex discharge of the urine. The mass reflex shows that the spinal reflexes have lost their local signature and have consequently become diffuse in their distribution.

In from one to five weeks after the flexor responses first appear the tone of the muscles of the limbs begins to recover and may be restored to a state close, but never equal, to that found in the normal individual. The posture of the limbs is one of slight flexion. At the same time the tendon jerks become elicitable. These are the only types of extensor response which have been observed in cases of complete transection of the human spinal cord. During this stage of recovery the contents of the rectum and bladder are voided automatically (Head and Riddoch[102]).

The chief difference in the condition of the spinal man and of the spinal cat or dog consists in: (1) the character of the flexor response, which in man has lost its local signature, is diffuse, and is elicited from an abnormally extensive receptive field; (2) the flexor position of the limbs at rest; and (3) the absence of extensor responses, i.e., of those responses

significant in maintaining the upright position and in progression. It would appear from this that in man the higher centers in the brain have taken over control of the integration of spinal reflexes to the extent of determining the local signature and limiting the spread of these responses and of governing the activities of the extensor muscles in maintaining postural tone and the extensor movements of progression, whereas in the lower mammals these phenomena may be executed by the spinal cord alone.

THE DECEREBRATE (BULBOSPINAL) ANIMAL

If the brain stem is transected through the lower part of the mesencephalon so that the medulla oblongata remains connected with the entire spinal cord the resulting preparation is called decerebrate.* As we should expect, a decerebrate animal is capable of more complex behavior than the spinal preparation. In contrast to spinal transection, decerebration is not followed by any depression of the simple spinal reflexes. Immediately after separating the bulbar region from the cerebrum one may elicit, in rabbit, cat, dog, and monkey, all those spinal reflexes which have been described in the preceding

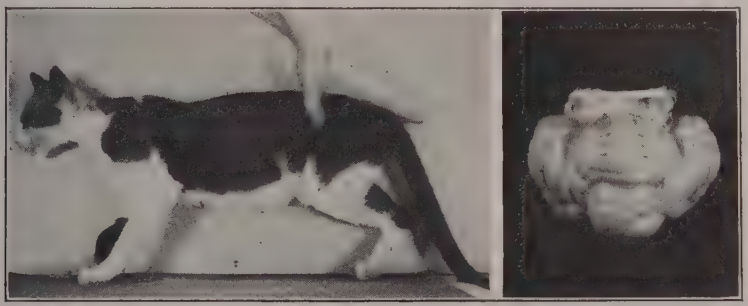

Fig. 41.—At left, photograph of a cat taken thirty hours after *decerebration* (with full aseptic precautions). Note that the sustained contraction of the limb extensors is sufficient to support the weight of the body and that the head and lower jaw are held up against the force of gravity. As indicated, the animal cannot stand unless balanced; the moment the hand was withdrawn the cat toppled over. At right, photograph of the dorsal aspect of the brain after removal from the animal. All parts rostral to an intercollicular transection of the brain stem had been removed at operation.

section of this chapter. Indeed there is enhancement, as regards excitability and execution, of all extensor reflexes, while, reciprocally, the flexor response has a higher threshold than in the spinal state. Thus the decerebrate animal exhibits a vigorous activity of the very reflexes which are most affected by spinal shock. In fact, without any external stimulation the extensor muscles remain in a state of steady contraction. Further examination shows that the entire system of musculature which posturally resists gravity in the standing position is in a state of increased tonic activity. This is spoken of as *decerebrate rigidity*.

The abnormal distribution of tone in the muscles of the body continues regardless of the position of the animal. If placed upright it remains standing provided it is balanced (Fig. 41), but a normal relation to the force of gravity is

*Following Sherrington and in accord with the proper definition of the word *cerebrum*, the adjective *decerebrate* is used to designate the condition which ensues upon mesencephalic transection of the brain stem. Decerebration is to be distinguished from *decortication*, or removal of the cerebral cortex (compare Figs. 41 and 43).

not at all necessary for the continuance of the rigidity. The extension of the legs and retraction of the head persist, even becoming stronger, when the preparation is put on its back. This caricature of normal standing represents the overactivity of that part of the central mechanism for standing which remains after mesencephalic truncation of the brain. With the rest of the brain intact it is modified and held in check by higher levels whose function it is to bring about the finer adjustments of posture. Since the rigidity may persist for many days,[156] it is not the result of some stimulation connected with cutting through the brain stem. It is therefore a release phenomenon whose intimate nature will be discussed in Chapter XIV.

Further examination of the freshly decerebrated animal reveals the presence of several capacities for response which are absent from the spinal preparation. Reflexes can be evoked which actuate the neck, trunk, and the four limbs as a whole, thus producing an attitude of the body which is definitely related to the place and quality of the stimulus. In the spinal animal, nociceptive stimulation

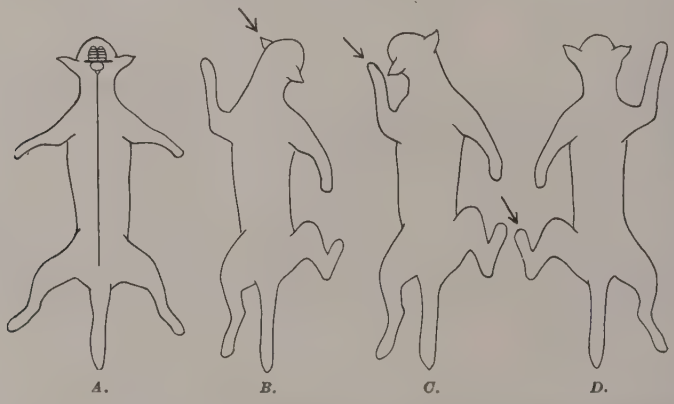

Fig. 42.—Reflex figures. *A*, the position of the cat in decerebrate rigidity. *B*, *C*, *D*, respectively, are the reflex figures resulting from stimulating the left pinna, the left forefoot, and the left hind foot. (After Sherrington.)

of a hind foot leads to ipsilateral flexion with crossed extension. In the decerebrate animal such stimulation gives, in addition, extension of the ipsilateral foreleg and flexion of the contralateral foreleg. If one pinna is stimulated the head and legs respond in the way shown in Fig. 42. Such groups of responses lead to the formation of *reflex figures* which may be considered to be compensatory, inasmuch as in each the movement of certain parts is adapted to restore the balance disturbed by the movement of other parts, and the result is an orderly change in the position of the body as a whole which is significant in meeting the exigency that has given rise to the reflex response. The reflex figure which is shown in *D* of Fig. 42 might be brought into play, for example, when a cat steps on some object which hurts its hind foot. The foot is lifted from the ground and the weight of the hind quarters is thus thrown on the contralateral hind leg, which extends to support this weight. At the same time the cat must prepare to move away so that the stimulus may not be encountered again, and for this act the extension of the crossed hind leg and

of the ipsilateral forefoot, with their backward thrust, tend to throw the body forward and support it while the flexion of the stimulated hind leg and the crossed foreleg move these limbs forward preparatory to supporting the body at the next step. The reflex figure is seen from this to be an integral mechanism out of which is built the functional act of stepping away from a stimulus which endangers the hind foot.

In spite of its ability to stand and to prepare attitudinally for progression, the decerebrate cat or dog cannot right itself, assume a sitting or standing position, run, walk, or jump. Neural mechanisms essential for these more complex acts are situated rostrally to the bulbar and lower mesencephalic regions. A strong nociceptive stimulus applied to a decerebrate animal may bring forth certain responses expressive of anger or rage. The animal may, for example, struggle, claw, bite, show erection of hair, widening of the eyes, and so on, but these pseudaffective reflexes never amount to an effective action of attack or escape.[203, 234] Here again we observe the mere rudiments of a normal mode of behavior. The integration of the full expression of anger depends, as we shall note, on parts of the brain which have been removed.

In the freshly decerebrate animal arterial pressure remains at or above the normal level, and compensatory cardiovascular reflexes can be elicited in normal fashion. Abolished almost entirely, however, are those bodily responses which assure, in the normal animal, the maintenance of a constant blood temperature in the face of environmental cold and heat (see Chapter LIX). The decerebrate cat or dog does not pant or shiver; neither does it display the changes in cutaneous blood vessels by which the thermal constancy of a normal animal's internal environment is supported.

THE DECORTICATE ANIMAL

When the ablation of cerebral tissue is limited to the most recently acquired part of the cerebrum, its mantle or cortex, the deficiencies are far less than those produced by mesencephalic transection. An outstanding abnormality of such mammals is the loss of modes of behavior dependent on past experience. All that has been learned disappears, and new types of response can be induced only by special methods of training.* This combination of a loss of what are ordinarily regarded as signs of higher nervous or mental functions with retention of many complex activities was first established experimentally in 1892 by Goltz[290] who succeeded in keeping alive for many months a dog from which he had removed all cerebral cortex. Goltz's achievement has since been repeated, and there are available descriptions of a number of decorticate cats and dogs.[269, 279, 309] As a result we have considerable knowledge of the capacities of such preparations.

The decorticate cat or dog walks, sits, crouches, and rights itself in fairly normal fashion. These activities are not interfered with by the abnormal and excessive postural contraction of the antigravity group of muscles which is the distinguishing feature of the decerebrate preparation. Nevertheless, when decorticate animals are held suspended they do exhibit, so long as they are quiet, a marked extensor rigidity, and it is probable that this is precisely the same

*Conditioned reflexes can be established in decorticate cats and dogs, but this requires special methods. There is available at present no evidence showing that wholly decorticate carnivores ever develop learned responses under laboratory conditions in which the normal animal readily acquires them.

thing as decerebrate rigidity.[269] The entire brain stem is not necessary for quadrupedal locomotion or for righting. The essential neural mechanism or "center" probably extends only as far forward as the caudal extremity of the diencephalon, since if only this region is left connected with the mesencephalon the paralysis of progression and righting seen after decerebration is replaced by an ability to walk, run, and keep right side up.[166] The execution of such behavior entails the repression of the bulbospinal mechanism whose overactivity in isolation fixes the decerebrate animal and the suspended decorticate animal in a posture of exaggerated standing.

After removal of the cortex, responses may still be obtained by stimulation of the special organs of sense located in the head region. Provided the rhinencephalon remains connected with the olfactory bulbs, the animal will react to certain olfactory stimuli. Exploratory activity, licking, and mouth movements result when an odoriferous food is placed near the animal. On the other hand, if olfaction is rendered impossible by extirpation of the bulbs or rhinencephalon,

Fig. 43.—At left, photograph of a *decorticate* cat taken five months after the cerebral removal. Note crossed position of forelegs, one of the typical postural abnormalities exhibited by animals after decortication. At right, photograph of dorsal aspect of the brain removed when the cat was killed after a survival of eleven months. (This is a cat, No. 244, described in the paper by Bard and Rioch.[269])

placing food on the tongue or in the mouth elicits licking, chewing, and swallowing. The presence in the mouth of highly unpleasant substances, such as quinine, induces vigorous attempts to get rid of the offending material. Indifferent materials are usually swallowed. Auditory responses are obtained when the diencephalic connections of the cochlear system remain. There may even be retained some ability to localize the source of certain sounds.[269, 279] On the other hand, the only visual responses which can be obtained after complete decortication are pupillary constriction and closure of the lids in response to bright illumination of the retinas.

In sharp contrast to the decerebrate animal the cat without cerebral cortex shows a capacity to regulate its temperature which is essentially normal.[275, 269] The chronically decorticate dog may fail to pant in normal fashion when

exposed to moderate heat; other thermal responses are modified (as in the cat), but not to an extent which renders the animal in any sense cold-blooded.[255] Although it has often been claimed that visceral functions are profoundly modified by decortication, a careful study of a number of decorticate cats and dogs during long survival periods has shown that such modifications as may have been present were not of a magnitude sufficient to interfere with general health.

Much interest attaches to the capacity of decorticate animals for displaying the signs of the more primitive emotions, anger, fear, and sexual excitement. The nature of the behavior attending these affective states is such that one would expect it to be controlled by the older and lower parts of the central nervous system. Like the simpler reflex acts it is a prompt response to the appropriate stimulus and is apt to take precedence over other modes of action; it remains uniform throughout most of life; and like many reflexes it serves a purpose essential for the preservation of the individual or species. The study of decorticate animals has shown that, although the neural processes underlying emotional consciousness may be cortical, the full complement of bodily changes which constitute the behavior of an enraged animal is due to a discharge of subcortical origin. Goltz's dog barked, growled, and made vigorous attempts to bite when disturbed in various ways. When submitted to trifling stimulations the similar dog studied by Rothmann[309] went into a fit of activity which closely resembled the picture presented by an enraged normal dog. When disturbed in various ways the long surviving decorticate cats prepared by Dusser de Barenne[279] and by Bard[267, 269] displayed typical feline rage responses. Evidence has been obtained to show that this type of patterned motor activity is dependent on a definite central neural mechanism located in the caudal part of the hypothalamus.[234] The excessiveness and easy elicitation of these rage responses lead to the conclusion that decortication releases the lower mechanism from an inhibitory influence exerted by the cortex. From this it does not follow that the cerebral cortex is not important for the execution of this type of emotional expression. As the organ of association it vastly increases the number of emotional stimuli, and it directs the "blind" activity of subcortical origin toward effective ends. Behavior quite similar to that of a terrified normal animal may be induced in surviving decorticate cats and dogs and, in the case of the female, typical signs of sexual excitement are displayed during estrus.[267, 269]

Wholly decorticate primates have not been adequately studied, for they are extremely difficult to prepare, but the experiences of several workers show that in the monkey removal of the frontal lobes alone results in deficiencies which are far more profound than any displayed by wholly decorticate carnivores. On the other hand, decortication in rabbits and rats is definitely less disturbing than it is in cats and dogs. Comparative studies thus emphasize the fact that "corticalization" of function has occurred in the progressive development of the mammalian brain.

CHAPTER XII

CONDUCTION IN THE CENTRAL NERVOUS SYSTEM; THE REFLEX ARC

So far conduction has been considered only with regard to the propagation of excitation through single neurons. In the central nervous system all pathways are broken by synapses, and impulses must pass from one neuron to another. It is often stated that this arrangement may impose certain characteristics on central conduction which do not appear in conduction in peripheral fibers. But the more one studies central conduction the less it appears to be fundamentally different from peripheral conduction. Nevertheless the central pathways are tremendously complex, and it is this feature which makes study of central mechanisms so difficult. Analysis demands that central conduction be studied in as simple a form as possible. For this reason much attention has been devoted to the spinal reflex arcs (Fig. 2) because in them the relation between afferent impulses and motor discharges can be fairly easily made out. Recently studies of transmission of impulses through the cranial motor nuclei which innervate the extrinsic muscles of the eye have richly supplemented knowledge gained from analysis of spinal reflexes. Also information of significance for our understanding of central conduction has been obtained by studies of transmission across synapses in the peripheral ganglia of the sympathetic system. Although a study of these relatively simple mechanisms does not constitute a comprehensive examination of central conduction, there is reason to believe that it gives a fair sample of the fundamental principles on which all central activity proceeds.

CHARACTERISTICS OF CONDUCTION IN THE REFLEX ARC

Irreversibility.—In nerve fibers it has been seen that impulses may spread in either direction along the axon. In the reflex arc as a whole the passage of the impulse is in one direction only, from the afferent or sensory neuron to the efferent or motor neuron. This is because the synapse possesses a valvelike action which imposes a polarity on the direction of conduction. Long before the existence of neurons or synapses was recognized this fact was foreshadowed in the joint discovery by Bell (1811) and Magendie (1822) of the entirely different functions of the spinal roots. That impulses do not spread backward from the motor to the afferent neurons can be demonstrated by leading off from electrodes applied to the dorsal root, when it will be found that no action current appears in the afferent fibers on stimulating the central stump of the divided ventral root.

Efferent Discharges in Dorsal Spinal Roots.—The principle of forward conduction in the central nervous system, i.e., the idea that centripetal impulses set up in primary sensory neurons pass only to central or motor neurons but never back to sensory neurons, has usually been regarded as an integral part of the Bell-Magendie law of the spinal roots. It is, however, a concept which is contradicted by a number of experimental facts. It has

long been known that stimulation of the peripheral end of a cut dorsal root may produce dilatation of blood vessels in the part of the body supplied by the fibers of that root (see Chapter XXXII) and it has been reported that a discharge of vasodilator impulses over dorsal root fibers may be provoked reflexly by stimulation of other afferent fibers, e.g., the depressor nerve (see Chapter XXXIII). Matthews[145] and Barron and Matthews[109] have obtained oscillographic evidence that impulses leave the spinal cord by way of the dorsal roots when spinal sensory fibers are stimulated. The occurrence of such discharges over lumbar dorsal roots and in the sensory fibers of the saphenous nerve as a normal part of various spinal reflexes has recently been established by Toennies.[151, 152] He found that at least 35 per cent of the large A fibers and many smaller fibers in the dorsal root are involved. The reflex discharges can be set up by ipsilateral and contralateral stimuli and they have all the essential characteristics of reflexes mediated by the ventral roots. They show central latencies of 4.0-5.5 msec. and are subject to summation, facilitation, after-discharge, and inhibition. Further, they are evoked by physiological stimuli such as tapping the skin or the patellar tendon.

The question of the location of the cell bodies of the fibers involved in these efferent discharges over dorsal root fibers has been a subject of considerable discussion and controversy which has recently been very adequately summarized by Hinsey.[128] One group of workers has maintained that the centrifugal impulses are carried by fibers of intraspinal origin which enter the dorsal roots and either make synaptic connections with dorsal root ganglion cells or course outward into the peripheral nerves. Still another view (Barron and Matthews) has been that the discharge occurs, at least in part, over "recurrent" fibers, collaterals of fibers which have entered the posterior funiculi from adjacent or nearby dorsal roots and that these collaterals pass outward without making synaptic connections in the ganglia. In the absence of any good evidence that there are synapses in dorsal root ganglia and in the face of excellent evidence that after section of a dorsal root between the ganglion cells and the cord all fibers degenerate in the central portion of the root and no fibers degenerate in the distal portion (Hinsey;[128] Westbrook and Tower[153]), it seems reasonable to suppose that these efferent discharges occur over neurons whose cell bodies lie in the dorsal root ganglia. It remains a mystery how the central terminations of these neurons are activated within the cord. In discussing his results Toennies states: "The conclusion seems to be inescapable that fibers from the dorsal root ganglia make central synaptic connections with internuncial neurons of the cord in such a way that they can be reflexly excited with a resulting discharge of impulses toward the periphery of the body."

The functional significance of these discharges has not been determined. Presumably they occur over fibers which mediate sensation, but of this we cannot be entirely certain. The evidence concerning their participation in the normal control of the smooth musculature of peripheral blood vessels is not wholly conclusive. There is evidence that acetylcholine is liberated at their endings. Toennies[152] has recently shown that the number of afferent impulses set up in the saphenous nerve by a gentle tap of the skin is decreased if a reflex discharge of dorsal root origin passes over saphenous fibers just before the skin is stimulated. The most obvious explanation is that the reflex discharge of efferent impulses and the afferent impulses from receptors are carried by the same fibers. Another possibility is that there is a special system of centrifugally conducting dorsal root fibers which exert a conditioning effect upon sensory endings or receptors. While Toennies' experiments do not permit a decision between these alternatives they suggest that reflexly evoked dorsal root impulses may play some role in determining the extent of sensory discharges into the central nervous system. Thus it is possible that the work already done foreshadows important developments in our knowledge of sensory mechanisms.

Latent Period.—Anatomical evidence indicates that the shortest central path in any spinal reflex arc is scarcely greater than the distance between the point of entry of the afferent fibers and the point of exit of the motor fibers. Measurements of the interval elapsing between the moment of stimulation of an afferent nerve and the appearance of the action current in the motor nerve shows that, if the most direct central path is utilized, central conduction is slower than con-

duction in either the afferent or the efferent limb of the arc. This is indicated by the following results obtained in a study of the reflex time of the flexor reflex of a spinal cat (Creed et al.[117]):

Time for passage of impulses in 13.8 cm. of afferent nerve at 31.6 meters a second	4.4 msec.
Time for passage of impulses in 19.5 cm. of efferent nerve at 93 meters a second	2.1 msec.
Total time for peripheral path	6.5 msec.
Apparent latent period observed	10.4 msec.
Central reflex time	3.9 msec.

A series of such measurements showed that the central time of this reflex varies between 3.0 and 5.5 msec., being shorter the stronger the stimulus which is applied, a result which is explained on the basis of summation of afferent impulses (see below). Recently Renshaw[147] has measured the interval between stimulation of the most rapidly conducting A fibers of a dorsal root and the ensuing potential wave in the corresponding ventral root which signals the reflex motor discharge. On correcting this observed latency by subtracting the brief times consumed by extramedullary conduction in afferent and efferent fibers he obtained values for the central reflex time which varied from 0.65 to about 1.0 msec. In confirmation of the earlier results of Eccles and Sherrington (see Creed et al.,[117] page 36) Renshaw found that the central reflex time, determined on the basis of a second volley of afferent impulses which enters the cord within a very short interval (3.8 msec.) of a first or conditioning volley, may be as brief as 0.5 msec., *but not any shorter*. This reduction, like that due to increasing the strength of a single stimulus, is due to summation and will be explained below.

There can be little doubt that the most rapid reflex conduction possible through a segment of the cat's cord consumes 0.5 msec. The distance over collaterals of afferent fibers from the dorsum of the cord to the anterior horn is about 3 mm. If we assume that the entire distance of the intraspinal conduction is 5 mm., a central reflex time of 0.5 msec. means that the *average* rate of reflex conduction within the cord is 10 meters a second. In the case of Renshaw's experiments this is to be compared with a conduction velocity of about 80 meters a second in afferent fibers and of from 30 to 100 meters a second in efferent fibers. The central delay in conduction usually is attributed to slower conduction across synapses, but it may in part at least be due to slowed conduction in the unmyelinated and apparently attenuated terminals of the axon collaterals of the afferent fibers.

Synaptic Delay.—Following a method originally used by Lorente de Nó for measuring synaptic delay at the eye muscle nuclei of the brain stem Renshaw[147] has secured figures for the delay in the region of the synapses between the endings of premotor fibers (afferent or internuncial fibers) and the motor neurons of the ventral horn. He found that a single shock applied through small bipolar electrodes thrust into the ventral portion of one side of a cat's spinal cord gives rise to two prominent waves, *m* and *s*, in the corresponding ventral root (Fig. 44). Now it is obvious that a moderate stimulus delivered in this manner will excite two groups of elements: (1) some of the motor neurons of the ventral horn and (2) some of the premotor fibers which make synaptic connections with motor neurons. Impulses set up in premotor fibers would cause a discharge only in motor neurons which were not directly excited by the shock, for all those which had responded would be refractory at the moment these impulses impinged on them. The *m* wave (Fig. 44) signals the discharge of a practically synchronous volley of motor impulses produced by direct stimulation of motor neuorns, and it follows the

stimulus by an interval accounted for by conduction from the anterior horn to the recording electrodes. The second or *s* wave, due to a somewhat asynchronous volley, begins at an interval after the start of the *m* wave which varies from 0.6 to 1.0 msec. It is significant that the interval between the two waves cannot be decreased by more than 0.1 to 0.3 msec. by increasing the strength of the stimulus or by sending in a conditioning volley of impulses. Lorente de Nó[138] had previously shown that the average synaptic delay at ocular motor neurons is 0.7 msec. and cannot be made to vary beyond the range 0.5-0.6 to 0.8-0.9 msec. If we assume that conduction between the presynaptic points of stimulation and the motor neurons and over the dendrites and cell bodies of the motor neurons is not inordinately slow, this interval must represent very closely the duration of the synaptic delay. At any rate these experiments restrict the site of the central delay to the region of the synapse.

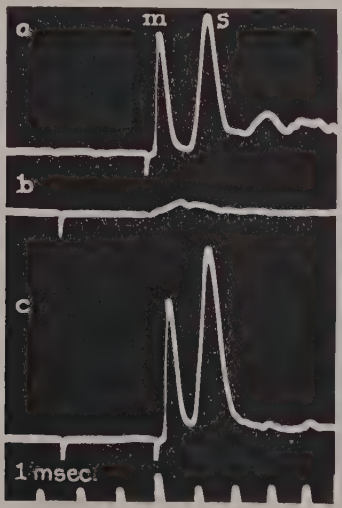

Fig. 44.—Measurement of synaptic delay at the motor neurons of the spinal cord. Cathode ray oscillograph records showing ventral root discharges, *m* and *s*, which follow stimulation of the cord through bipolar needle electrodes in the central gray matter. Decerebrate cat with cord sectioned at upper lumbar level. Stimulation at a segment well below transection. *a*, response to single shock applied through needle electrodes; *b*, to submaximal stimulation of ipsilateral dorsal root; and *c*, to needle and root stimulation combined. Downward strokes from baseline in *a*, *b*, and *c* signal stimuli. Lowermost record, time intervals of 1 msec. (From Renshaw: J. Neurophysiol. 3: 373, 1940.)

The correctness of the interpretation that the interval between *m* and *s* represents the duration of synaptic delay or of delay in the intimate vicinity of the synapses at the motor neurons is supported by two additional facts.[147] First, Renshaw found that the threshold of stimulation for the *m* wave is lower than that for the *s* wave when the electrodes are in the most ventral part of the cord while that for the *s* wave is lower when the electrodes are more dorsal in position. Second, as the stimulus is increased both waves increase in size until with very strong stimuli the *s* wave decreases as the *m* wave continues to grow larger. This effect of very strong stimuli is obviously due to the fact that so many motor cells are directly stimulated that very few are not refractory when the impulses set up in premotor fibers impinge upon them.

Histological studies (see Fulton,[124] page 57) have indicated that the majority of dorsal root fibers terminate on internuncial neurons and that only a

small number make direct synaptic connections with the motor cells of the ventral horn. According to this evidence most spinal reflexes must involve at least one intercalated neuron (see Fig. 2). But comparison of the shortest central reflex time with the duration of the synaptic delay at the motor neurons shows that there are spinal reflex arcs of two neurons (one synapse). On the basis of the figures given above we may suppose that an arc of three neurons (two synapses) would show a central reflex time which could never be less than 2 × 0.5 msec. and might vary between 1.0 and 2.0 msec. But as Renshaw points out, it is impossible to state whether a discharge in motor neurons after a central delay of 2.4 msec. represents activity in arcs of three synaptic relays with an average delay of 0.8 msec., or in arcs of four relays where the average delay is only 0.6 msec. or in both types of pathways.

Summation.—We have already encountered two different types of summation, summation of inadequate stimuli and summation of contractions. Reflex conduction provides us with a third type, *summation of afferent impulses.* A volley of impulses in a few afferent nerve fibers frequently fails to produce a reflex discharge which can readily be brought about by two or more such volleys or by a single volley in a larger number of fibers. It is evident that the threshold of some excitatory process in the central region is reached only when a certain number of afferent impulses enter the cord within a given interval of time. This form of summation is therefore very similar to the phenomenon of summation of inadequate stimuli observed in peripheral nerve and muscle. Two types of summation of afferent impulses, spatial and temporal, have been described.

Spatial Summation and Subliminal Fringe.—Physiological evidence emphasizes the great importance of this form of summation in the central nervous system and histological facts show that abundant structural provisions have been made for its occurrence. The dendrites and cell body of an individual neuron not only have multiple contacts with each presynaptic fiber (Fig. 3) but are connected in this way with many such fibers (principle of convergence).

Spatial summation may be readily demonstrated in any case where an adequate volley of impulses over either of two afferent nerves produces a reflex contraction of some muscle. If the stimuli applied to the two nerves are made so weak that the volley set up in either is not alone adequate to evoke a reflex motor discharge, a response will be obtained when the two stimuli are applied simultaneously or at a very short interval apart. The reflex response is smaller the longer the interval, and it disappears, in the case of a typical spinal cord reflex, when the two volleys are separated by more than about 15 milliseconds; it is greatest when the two stimuli are simultaneous. Such results show that an afferent volley which is unable to evoke a reflex discharge does set up a brief and rapidly decaying subliminal excitatory process in some of the central neurons. Neurons undergoing this change are said to be in the *subliminal fringe of excitation* (see Fig. 48). Subliminal fringe, as the term is usually used, is a physiological concept based on the anatomical fact that the afferent fibers to any group of neurons (neuron pool) branch in such a way that they partially overlap in making synaptic connections. Consequently, whenever a few neurons receive enough impulses to be liminally stimulated other neurons are subliminally stimulated and constitute the subliminal fringe. Effective summation occurs when the subliminal excitation set up by one group of afferent impulses is sufficient to bring that produced by another group of afferent impulses to the threshold level. Summation determines not only whether any reflex discharge occurs but also the

number of motor neurons discharging and hence the magnitude of a reflex contraction. If, for example, in the situation depicted in Fig. 48 impulses should enter the neuron pool from a third source and exert a subliminal effect on cells in those parts of the fields of *a* or *b* which do not overlap they would tend to recruit additional discharges over neurons whose cell bodies lie in this subliminal fringe.

The length of the period during which two groups of impulses arriving at a motor neuron may produce summation is apparently very brief. The most exact experimental determination of its length has been achieved by Lorente de Nó in a study of transmission of excitation through cranial motor nuclei. He found that when two volleys are delivered to a motor nucleus over two different paths summation is optimal when the volleys arrive simultaneously, very much reduced when the interval is as short as 0.15-0.2 msec., and nearly absent when the separation is no more than 0.5 msec. This maximal summation interval is equal to the minimal synaptic delay[138] which in turn is equal to the duration of the major part of the spike potential at the synaptic knobs of the presynaptic fibers. It is also of the same order of magnitude as the absolutely refractory phase of the motor neurons (see below).

The great importance of spatial summation is brought out by evidence indicating that threshold excitation of an individual central or motor neuron is never achieved unless several impulses are delivered simultaneously or nearly simultaneously at several synapses (synaptic knobs) on the dendrites or cell body of that neuron. There appear to be differences between pathways in the average number, density or size of the synaptic endings which they make on central neurons. On the one hand is the case studied by Lorente de Nó,[136, 137] that of a fiber bundle (the posterior longitudinal bundle) which connects directly with the cells of the oculomotor nucleus; a single volley in a few of its fibers suffices to produce a motor discharge, provided other pathways to the nucleus which are normally continuously active are intact, but if these sources of subliminal excitation are interrupted, even a maximum volley in the bundle fails to cause a discharge over third nerve fibers. Here it is evident that the presynaptic fibers do not make sufficient synaptic connections with individual motor neurons to permit effective summation to occur. On the other hand, there is the case of a two-neuron (one synapse) spinal reflex arc in which a single synchronous volley over afferent fibers suffices to evoke a motor discharge. Here we must suppose that individual anterior horn cells have relatively rich synaptic relationships with the dorsal root fibers.

The histological correlates of this conception have been rigorously defined by Lorente de Nó.[142] He has especially sought an understanding in anatomical terms of the fact that although "threshold stimulation demands convergence on the neuron of several impulses – – – – – – large volleys, indeed very large ones, may remain ineffective, while a few of the impulses which they contain, when added to impulses carried by other fibers, do set up a response." Lorente de Nó[139, 142] points out how well all the known facts about synaptic transmission fit the hypothesis that threshold stimulation of a neuron takes place whenever all or at least a majority of the synaptic knobs over a discrete zone of the neuron are activated simultaneously. In other words, spatial summation can occur only when impulses reach synapses which are close together on the cell body or dendrites. Now if a large volley is set up in fibers which have knobs scattered over the neuron and not concentrated in any one locus, it will only produce subthreshold excitation in a number of loci. If, however, impulses from another source simultaneously activate enough other knobs at one of these loci, the threshold will be reached and the cell will discharge an impulse.

Histological studies of central neurons show distributions of the synaptic knobs of different fibers which are entirely compatible with this assumption.[139]

It will be of interest to point out that this hypothesis of synaptic stimulation as a local process involves the concept that the individual synapse, i.e., the contact between an end knob and the underlying area of cell body or dendrite, is a region where the transmission of excitation undergoes decrement. The nerve impulse as an excitatory process is reduced to subthreshold value and as a consequence summation is required for transmission to occur.

Temporal Summation.—It has been shown that a reflex discharge in motor fibers may be produced by two successive volleys in the same afferent nerve when neither of them is alone sufficient to excite the motor neurons. To obtain this result the second volley has to follow the first within a very short interval, e.g., 4 to 6 msec. in the case of the flexion reflex,[117] and because of the refractory period of the afferent fibers this type of facilitation can be effected only within a narrow time range. Experimental facts of this kind, formerly described as examples of temporal summation, are now generally regarded as actually due to spatial summation effected, as described below, through interneurons. There is considerable doubt whether temporal summation of impulses arriving at a central synapse in succession over the same fiber or group of fibers is possible. This doubt arises from the studies of Lorente de Nó of the duration of the period of effective summation to which reference has already been made and in which it was found that the opportunity for summation has practically disappeared when two volleys delivered over different pathways are separated by an interval as short as 0.5 msec. From this it appears that the subliminal excitatory process set up at a central neuron has a duration of the same order of magnitude as the absolutely refractory period of the presynaptic fibers. If this is the case, a fiber could not deliver a second impulse in time to bring the excitation to the threshold level and consequently temporal summation is impossible. There remains the possibility that *subliminal* synaptic excitation by a volley of impulses may be followed by a delayed or second phase of lowered threshold during which summation by a subsequent volley conducted in the same fibers could occur (see below), but Lorente de Nó, while not denying this possibility, has been unable to demonstrate its development.[142] The changes in excitability, which follow *threshold* synaptic stimulation constitute a separate problem, discussion of which logically follows.

Excitability Changes in Central Neurons.—In Chapter VII the refractory periods, absolute and relative, and the subsequent supernormal and subnormal phases of nerve fibers (axons) were described. For an understanding of central conduction it is important to know whether these changes in excitability occur in the cell bodies and dendrites of motor and other central neurons. The question is of significance in deciding whether the cell body and dendrites possess properties which differ in any fundamental way from those of axons.

Refractory Periods.—For reasons that should be apparent to the reader of the preceding paragraphs the problem of changes in the excitability of the central neuron after adequate synaptic stimulation cannot readily be investigated by studying the effects of successive volleys of afferent impulses. A means of measuring the absolutely and relatively refractory periods of spinal motor neurons was devised by Denny-Brown.[117] It involves the sending of a volley of antidromic impulses up motor nerve fibers and therefore is called the *antidromic shock technique.* If, after section of appropriate dorsal roots, a single

shock is applied to a peripheral nerve, the only volley of impulses which will reach the spinal cord will be the one conducted centripetally in the motor fibers. Since there is every reason to believe that an antidromic impulse spreads beyond the proximal part of the axon into the cell body (see Erlanger and Gasser,[47] page 204), we may expect that on dying out there it will be followed by a refractory state. The course of central refractoriness may therefore be tested, at least roughly, by sending an afferent volley into this same pool of motor neurons at various intervals after the arrival there of the antidromic volley. In this way it was determined that a single afferent volley does not evoke a reflex discharge within 5 msec. of the arrival of an antidromic volley, and that from 10 to 15 msec. are required for full recovery of the normal responsiveness of the motor neurons to synaptic stimulation.[117] The unresponsive period of 5 msec. was not regarded as the duration of the absolutely refractory period, because it is impossible to stimulate a relatively refractory neuron maximally by an afferent volley; it was estimated that this period must be less than 2.5 msec. Employing the same technique in the somewhat simpler case of the oculomotor neurons Lorente de Nó[142] found that a volley in the posterior longitudinal bundle first becomes effective when it arrives at the motor neurons 0.43 msec. after the antidromic volley. He therefore believes that the absolutely refractory period of the cell bodies and dendrites of these neurons is not greater than about 0.5 msec. and emphasizes this as the upper limit of the interval during which the synaptic excitatory process can remain at full value. The conclusion is drawn that "in the whole synaptic arc there are no elements (synaptic endings or motor neurons) with an absolutely refractory period longer than that of the presynaptic axons themselves." The relatively refractory period of the ocular motor neurons appears to be 13 to 20 msec., about the same as that of the spinal ventral horn cells.

Subnormality.—At this point the reader must bear in mind the facts about the later changes in excitability which occur in peripheral axons following the passage of an impulse (see Chapter VII and especially Erlanger and Gasser[47] and Gasser[126]). As shown in Fig. 16 on page 22 the rising curve of excitability which marks the relatively refractory period continues upward after reaching the normal level and remains above normal for a short time (about 15 msec. in mammalian A fibers). Immediately after this the excitability curve drops below normal and continues for some time (70 msec. or more in A fibers) at a subnormal level (not shown in Fig. 16). These two periods are coextensive with the after-potentials (see Figs. 28 and 29); during the negative after-potential the axons are supernormal, and during the positive after-potential they are subnormal. The supernormal period and the negative after-potential are seen only when activity is restricted to one or a few impulses; they do not appear after tetani. On the other hand subnormality, and with it the positive after-potential, is increased and prolonged by a tetanus. This is known as *summation of subnormality*. It may raise the threshold 30 per cent and endure for very considerable periods of time. Gasser has reported durations of subnormality of a minute or more. A high frequency of response is especially effective in prolonging this state.

Turning to the central nervous system, it can now be said with assurance that motor neurons have a subnormal period similar to that of axons and are subject to summation of subnormality. In the case of the spinal anterior horn cells this has been clearly demonstrated by Eccles and Pritchard[121] and by Gasser[126] who found that the backfiring of an antidromic volley of impulses in a

ventral root evokes a spike followed by a positive potential of central origin.* When a tetanus is backfired into the cord the series of spikes is followed by an increased and prolonged positive potential which has practically the same form as that shown in Fig. 29 on page 45. Here is evidence of summation of subnormality in central neurons. That this positive potential recorded from the spinal cord denotes subnormality in that part of the motor neuron which responds to presynaptic impulses is demonstrated by the fact that an afferent volley entering through the dorsal root of the same segment evokes a smaller reflex discharge throughout the period during which the positive potential following an antidromic volley persists. No evidence of supernormality could be obtained.[126] The relatively refractory period appears to fuse with the subnormal phase without interposition of a transient period of lowered thresholds. In this respect central neurons seem to differ from peripheral axons.

The ocular motor neurons also recover from refractoriness through a phase of depressed excitability which lasts much longer than the relatively refractoy period of the peripheral axons. An investigation (Lorente de Nó and Graham[143]) by means of the antidromic shock technique has shown that this phenomenon is nothing other than a subnormal phase comparable to that of axons. After one response the ocular motor neurons, which are extremely "rapid" elements, go through a period of depressed excitability which lasts at least 30 msec. Two responses in rapid succession produce severe and long-lasting subnormality. Summation of subnormality is easily demonstrated. Although a supernormal phase appears in the fibers of the motor neurons after the passage of an impulse set up by synaptic stimulation, no corresponding period of increased excitability appears to develop at the synaptic ends of these units. It is possible that supernormality actually develops in the cell body and dendrites of central neurons, but is obscured by various factors.

At present the whole question whether synaptic excitability rises above normal after the discharge of an impulse and so renders the cell more susceptible to stimulation by subsequent impulses is under investigation, but to date no results have been obtained which warrant further discussion here. On the other hand, we have every reason to stress the fact that subnormality and summation of subnormality take place at the synapse. This fact is of special significance for a theory of central inhibition and is to be correlated with a group of other facts to which we must now turn our attention.

The Role of Internuncial Neurons.—One very obvious histological feature of the central nervous system is that it has ample arrangements for the passage of impulses from afferent fibers to motor neurons by various indirect paths made up of internuncial neurons. The two fundamental types of internuncial circuits are diagrammatically represented in Fig. 45. Their functional significance is so great that no physiological treatment of the nervous system can afford to neglect a consideration of activity in them. Here it will be possible to consider only

*These potential changes were recorded by two electrodes, one on the side of the ventral root and the other on the cord adjacent to the point of emergence of the root. This arrangement records specifically the potential changes in the intramedullary portions of the ventral root neurons. For example, it was found that after asphyxiation of the cord the large potential disappears and there is left only the after-potential of the root fibers. Gasser points out that "under the conditions of the experiment, the centrally contributed portion of the potential so dominates the contribution from the root that in the algebraic summation of the two in the records, the configuration of the centrally produced potential is not obscured." It should be pointed out in this connection that this method of recording does not pick up changes due to activity in afferent or internuncial neurons. Potentials arising from these elements can, however, be recorded by a different arrangement of electrodes, e.g., both on the cord itself (see the section of this chapter entitled "The Potentials of the Spinal Cord").

some of the more obvious consequences of these arrangements. Others will be referred to in connection with specific topics.

The important feature of internuncial neurons is not that they are intercalated between afferent fibers and motor cells, as is the internuncial neuron labelled *e* in Fig. 2 on page 5, but that "they form collateral chains superimposed upon the shortest path which, if a sufficient background of facilitation exists, is undoubtedly passable (Lorente de Nó[140]). The implication is that the background of facilitation is supplied by impulses in internuncials.

Evidence has been presented above that the excitatory process set up at the synapse by a single presynaptic impulse is so brief that it cannot provoke a repetitive discharge of impulses in individual motor neurons. Yet it is fully established that when a single large volley enters the spinal cord over dorsal root fibers many motor neurons discharge repetitively (after-discharge) and the muscle may receive impulses for 100 msec. or longer.[117] The only explanation of this which is in accord with established facts is that spreading of the original single volley of impulses over chains of internuncial neurons such as are indicated in *M* of Fig. 45 leads to the delivery of a succession of impulses at the motor neurons. The fact that in the case of a sympathetic ganglion, where there are no internuncial neurons, a single volley of impulses in preganglionic fibers

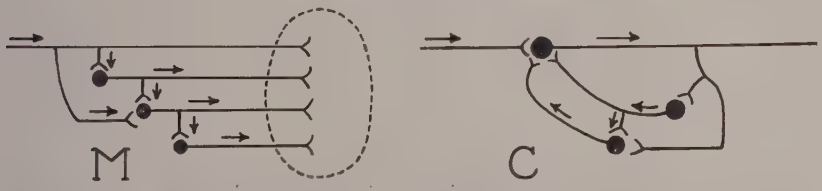

Fig. 45.—Diagrams of the two types of chains formed by internuncial neurons: *M*, multiple chain, and *C*, closed self-reëxciting chain. (From Lorente de Nó: J. Neurophysiol. **1**: 207, 1938.)

initiates only a single volley in postganglionic fibers emphasizes the cogency of this interpretation. The concept of a long-lasting stimulation by impulses delayed during their passage through internuncial neurons and synapses is not new; it was introduced by Forbes[122] in 1922 and has been elaborated by numerous authors. The recent emphasis put upon it by Lorente de Nó[140, 142] is based on the correlations which he has been able to make between physiological occurrences and established anatomical arrangements. Two lines of evidence demonstrate the actual production of sustained excitation of motor neurons by activity in internuncial chains.

The Potentials of the Spinal Cord.—It was first shown by Gasser and Graham[127] that when a volley of centripetal impulses is fired through a dorsal root a sequence of definite potential changes develops in the spinal cord. The dorsum of the cord just above the level of entry of the root becomes, in respect to the ventral surface or to more rostral levels, first negative and later positive (Fig. 46). The initial event is a negative spike which can be interpreted only as a sign of synchronous impulses in the intramedullary extensions of the dorsal root fibers. It has the duration of the spike of peripheral A fibers. The negative and positive potential waves which follow are like the after-potentials of peripheral nerve, but they are larger. This and a number of other facts show that they

do not arise in the central portions of the dorsal root fibers. Since, with the electrode arrangement used for their study, an antidromic volley in a ventral root gives only a spike, they are not due to after-potentials or other changes in motor neurons. Therefore by a process of exclusion they can be attributed to the internuncial neurons of the cord. Gasser has given excellent reasons for believing that the negative potential, which is usually double (as in Fig. 46) and sometimes complex, is formed by the temporal dispersion of spike potentials in internuncial neurons and that the positive cord potential is due to the ensuing positive after-potential in these same neurons.

The importance of the cord potentials warrants a more detailed description of the evidence upon which this interpretation of their origin is based. Reasons for excluding the intramedullary portions of the dorsal root afferents as sources of the true cord potentials can best be presented in Gasser's own words: "If two roots are stimulated, or two branches of the same root, the potentials produced by the components will add as long as they arise in parallel pathways, but they will fail to do so when the pathways converge onto common lines. The intramedullary spikes do as a matter of fact add; but the potentials which follow them do not add. The potentials evoked through simultaneous stimulation of two branches of a root are but slightly larger than those evoked through stimulation of one of the branches alone. This means that the cord potentials arise in units other than those which

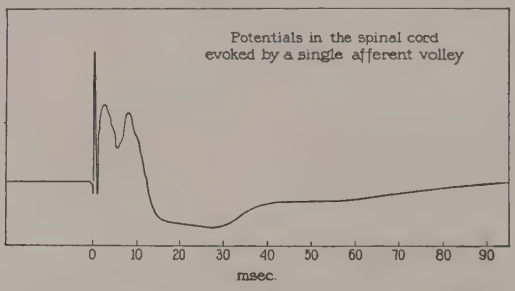

Fig. 46.—Cord potentials evoked by a single volley in dorsal root fibers. Leading-off electrodes on surface of cord. Upward deflection indicates negativity in active region. Appearing in order are (1) an initial negative spike, (2) a much more prolonged negative potential which, as is usually the case, shows two irregular waves, and (3) a relatively large and long positive potential. (From Erlanger and Gasser: *Electrical Signs of Nervous Activity*, Philadelphia, 1937, University of Pennsylvania Press.)

produce the spikes and that, therefore, they occur beyond the first neurone, with either motor cells or internuncial neurones to choose from" (Erlanger and Gasser,[47] page 188). Although, as we have seen, activity in spinal motor neurons is followed by a positive after-potential, these elements do not contribute to the cord potentials under discussion, for an antidromic volley in the ventral root gives a spike but does not evoke a typical cord potential when the electrodes are arranged in such a way that one is recorded when an afferent volley is set up. The only possible source remaining is the internuncial neurons of the cord.

If the long negative and positive waves, which are the essential features of the cord potential, are attributable to internuncial neurons, the simplest explanation is that they represent the sequence of potential changes in these elements. In individual internuncial neurons this would be a spike, perhaps with some negative after-potential, and then a positive after-potential. If, as is reasonable to suppose, these units discharged somewhat asynchronously, the temporal dispersion of spikes would give the negative part of the cord potential and the ensuing positive potentials would give the positive part. Hughes and Gasser found that when two volleys of afferent impulses are sent in at various intervals apart the second does not evoke any negative cord potential until it falls after the negative portion of the response to the first volley and a full-sized second negative cord potential cannot be obtained by a second volley until the positive phase following the first has run its course. This

behavior is strong evidence that the negative cord potential is formed by the summation of spikes, for, as Gasser points out, the neurons generating it would be unresponsive to further excitation as long as the potential lasts.

Study of the negative cord potential has supplied excellent evidence that sustained excitation of motor neurons may be brought about by impulses in internuncial neurons. For example, Hughes and Gasser (see Gasser[47]) were able to show that a motor discharge often occurs throughout the course of this part of the electrical response of the cord (Fig. 47). In certain experiments a dorsal root volley not more than 1 or 2 msec. in duration caused a motor discharge into the sciatic nerve which lasted 25 msec. (after-discharge) and was concurrent with the negative cord potential. Obviously in this case internuncials were supplying the stimulus for the discharge which long outlasted the excitatory effect of the primary afferent impulses which, as we have seen, does not last longer than 0.5 msec. In addition, the well-known facilitation of a second (testing) volley by a first (conditioning) volley was related to the

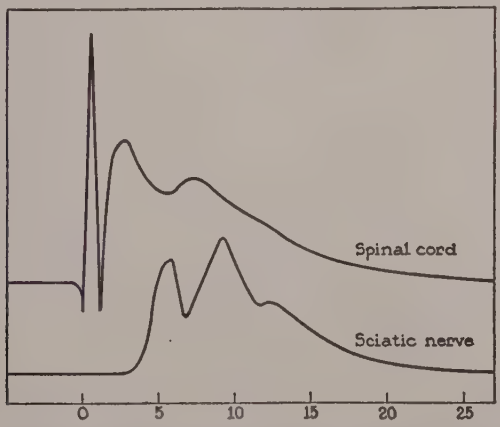

Fig. 47.—Comparison of the duration of the discharge of motor impulses into the sciatic nerve with the duration of the negative part of the potential evoked in the internuncial neurons of the spinal cord by a single afferent volley from a dorsal root. The experiment was performed on a cat under light ether anesthesia. (From Erlanger and Gasser: *Electrical Signs of Nervous Activity*, Philadelphia, 1937, University of Pennsylvania Press.)

negative cord potential. When the flexion reflex was facilitated (increased in magnitude) in this way considerable additional negative potential was evoked by the conditioning volley and the positive cord potential was small. This suggests that the second volley produces a greater reflex effect because its impulses arrive in the motor neuron pool concurrently with impulses set up by the first volley but delayed by passage through internuncials. The correlation between the positive cord potential, which signifies subnormality in internuncial neurons, and inhibition in the reflex arc will be discussed in a later section of this chapter.

Internuncials Acting on Ocular Motor Neurons.—Lorente de Nó[142] has been able to record impulses in internuncial neurons directly and to compare this activity with the discharge of motor neurons to a muscle. Micro-electrodes were inserted into a pool of internuncial neurons situated orally, laterally, and ven-

trally to the oculomotor nucleus; other leading-off electrodes were placed on the internal rectus muscle to record the responses of the motor neurons. Single or successive shocks were applied to the posterior longitudinal bundle just beneath the floor of the fourth ventricle. In this system the posterior longitudinal bundle can be regarded as an afferent pathway comparable to a dorsal root; impulses in its fibers are conducted not only directly to the oculomotor neurons but also indirectly through the pool of internuncial neurons whose activity was being observed. It was shown that a volley in the bundle was delivered to both groups of neurons and caused both to discharge impulses. Further, when two successive volleys, the first being smaller than the second, were set up, the size of the motor response and the amount of internuncial activity increased enormously, provided the second shock was delivered during the internuncial discharge due to the first volley. If the second shock was delivered after this burst of internuncial impulses had subsided, the motor response was not augmented. Such results are in full accord with those obtained in studies of the cord potentials and together they demonstrate quite conclusively that impulses detoured from a direct afferent path over internuncial chains can facilitate the stimulation of motor neurons by impulses of later origin which travel over the direct path.

We are now in a position to give an explanation of the fact that the central time of a spinal reflex is shorter when the testing volley of afferent impulses follows a conditioning volley at a short interval (e.g., 4 msec.), a result which indicates that the first volley somehow reduces the time required for the second to set up a motor discharge. Each volley on entering the cord will be conducted to the motor neurons both directly and over numerous internuncials as in *M* of Fig. 45. Unless the first volley is very large it will produce a motor discharge only because sufficient spatial summation is effected by the arrival of impulses which have consumed some time in passage over internuncial channels; for this reason the latency will be greater than that of a reflex produced by a larger single volley. Now if the second volley enters the cord within a sufficiently short interval after the first, those of its impulses which go directly to the motor neurons will arrive almost concurrently with the impulses of the first volley which have been delayed by passage over longer internuncial paths, and as a result effective summation will occur sooner than in the case of the first volley.

Internuncial Activity as a Source of Sustained Excitation.—The bombardment of motor neurons by internuncial impulses can be a source of continuous stimulation. In the absence of any clear indication that the central synapse is the site of any process of excitation other than that which develops and decays within about 0.5 msec. and occurs only as a result of the arrival of an impulse, we must attribute much to the activity of internuncial neurons. It ensures constant stimulation by the continuous arrival of impulses. Internuncial bombardment, be it understood, may produce either repetitive discharges in motor neurons by delivering impulses of threshold density or it may subject the motor neurons to rapidly repeated subliminal rises in excitability by impulses which are not dense enough to cause threshold excitation. The latter effect is important because it will facilitate any intercurrent stimulation.

The multiple or open type of internuncial chain (Fig. 45, *M*) can deliver impulses at high frequencies for brief periods of time. A longer lasting bombardment could be supplied by the closed type of chain (Fig. 45, *C*). Because the absolutely refractory period of the synapse is no longer than the synaptic delay, such a chain could be self-reëxciting and so maintain automatic activity, especially if it contained many links. When the links are few, the circulating impulse will arrive at each neuron so frequently that blocking by summation of subnormality or by fatigue is likely to occur. In any case occasional stimulation

by entry of impulses from some active region would cause it to furnish enduring bombardment. It can scarcely be doubted that much of the readiness of different parts of the central nervous system to respond to incoming impulses is maintained by continued activity in chains of internuncial neurons.

After-Discharge.—This characteristic is found in almost all reflexes. When a single shock applied to an afferent nerve elicits a motor response, the mechanical and electrical records of the contraction reveal repetitive discharges over the motor neurons. Since the stimulus does not set up more than one impulse in each afferent fiber, it follows that the motor neurons continue to discharge impulses for some time after the single volley of afferent impulses has entered the cord. In the case of the flexor reflex this after-discharge, as it is called, may last 100 msec. or longer. It is so pronounced in the crossed extensor reflex that mere observation of the limb movement suffices for its detection. In the flexor reflex it is not due to the contracting muscle reexciting itself reflexly through stimulation of proprioceptors by its own contraction, for it is not affected by deafferenting the muscle by section of the appropriate dorsal roots. In the crossed extensor reflex it is due partly to a proprioceptive autogenous excitation and partly to the purely central mechanism which operates in the case of the flexion reflex. We must conclude, therefore, that after-discharge is largely the result of prolonged excitation set up somewhere along the central pathways by individual afferent volleys. Since the evidence available shows that the excitatory process at the synapse is very brief and therefore cannot produce repetitive discharges of motor neurons (see page 100), we must explain after-discharge on the basis of some other process. As we have seen, there is excellent evidence that the phenomenon is the result of activity in chains of internuncial neurons.

Rhythm of Reflex Discharge and Reflex Tetanus.—A single reflex twitch probably never occurs normally. We have seen that even when the reflex stimulus is a single volley of afferent impulses, the motor neurons discharge repetitively. The rate of this discharge determines whether the reflexly contracting muscle undergoes a series of twitches, an incomplete tetanus, or a complete tetanus. When the reflex stimulus is repetitive, its rhythm may be detected in the motor discharge, but more often it cannot. In the spinal flexor reflex each volley of afferent impulses gives rise to a volley of efferent impulses, but between these are secondary discharges signalling after-discharge. In the crossed extensor reflex the rhythm of motor discharge is wholly independent of the stimulus rhythm, and it is clear that the rate of discharge is determined by the same central mechanism which is responsible for after-discharge.

If a sustained reflex tetanus is set up by a series of afferent stimuli, the tension may rise to a maximum as abruptly as when a tetanizing stimulus is applied to a motor nerve. This occurs in the spinal flexor reflex. Responses of this type are called *d'emblée* reflexes, and they are characterized by the fact that all the motor units engaged respond to the first stimulus of the series. At the other extreme is the slow increase of tension which characterizes the crossed extensor reflex. In this type the reflex tetanus develops so gradually that its maximum is not reached for a period which is often ten to twenty times longer than in the tetanus produced by motor nerve stimulation. This is the *recruitment* type of reflex response. Here repetitive afferent volleys cause more and more motor units to be recruited into the reflex. Obviously recruitment is a process related to summation of afferent impulses. It is attributable to an extension of the

same process which underlies the facilitating effect of the first of two afferent volleys upon the response to the second (see page 99). It may be thought of as the result of the development of threshold excitation in more and more neurons of the original subliminal fringe, probably through the agency of mounting internuncial activity.

Fractionation of the Reflex Center; Convergence and Occlusion.[117]—A reflex contraction of any single muscle can usually be produced by stimulation of a variety of afferent nerves. For example, the anterior tibial muscle contributes to the flexor response which can be evoked by stimulation of afferent fibers in any one of several nerve trunks. It is found, however, that the most powerful reflex contraction that can be obtained in the muscle by stimulation of any one of these afferent channels is never as great as the maximum motor tetanus. Hence one must conclude that no single afferent pathway has reflex access to all the motor units of the muscle and that only a fraction of the motor units take part in the response elicited from a single afferent nerve or from the receptors connected with that nerve. In other words, a reflex fractionates a muscle.

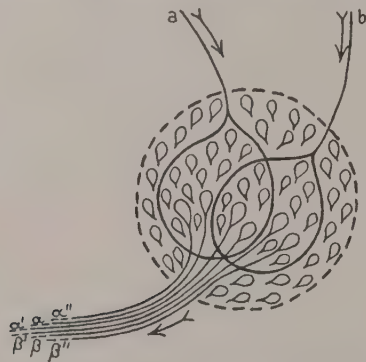

Fig. 48.—Diagram which may be used to illustrate both the subliminal fringe of excitation and the phenomenon of occlusion. The excitatory afferents, *a* and *b*, each connect with a number of the units which make up the motor neuron pool of a muscle. Axons are drawn for only four of the motor neurons activated by *a* alone (a'', a, a' and β') and by *b* alone (β'', β, β' and a').

Subliminal fringe is illustrated if it is considered that *a* alone or *b* alone can set up only subthreshold excitation in the motor neurons with which it is synaptically connected. When the two afferents are stimulated simultaneously, the fields of subthreshold excitation partly overlap and several motor neurons are activated by spatial summation to discharge over their axons. Thus impulses are set up over a' and β', but not over a and a'' or β and β'' which belong to neurons remaining in the subliminal fringe.

Occlusion is illustrated if it is considered that *a* and *b* are afferent channels each of which sets up threshold excitation in all the motor neurons with which it connects. When stimulated simultaneously they produce a contraction which is less than the sum of the contractions resulting from stimulation of *a* and *b* separately. This is because overlap causes a contraction deficit, e.g., a discharge occurs over a' and β' when either *a* or *b* is stimulated as well as when both are stimulated. (From Creed, Denny-Brown, Eccles, Liddell and Sherrington: *Reflex Activity of the Spinal Cord*, Oxford, 1932, The Clarendon Press.)

When the tensions of the reflex contractions of a muscle elicited from individual afferent nerves are added, the sum greatly exceeds the maximal tension which can be developed by stimulation of the motor nerve. Consequently, it must be that some motor units are excited from more than one afferent nerve. The central terminations of these different afferent paths must converge on to the same motor neuron. This *principle of convergence* constitutes an important basis of coordinated function in the nervous system. It means that a motor unit is the

common tool of influences of diverse origins. The results of histological studies are in harmony with the physiologically derived evidence for a wealth of convergence in the reflex pathways of the spinal cord. And, as a matter of fact, a more general consideration carries one to the same conclusion; a great many more sensory fibers enter the spinal cord than there are motor fibers leaving it. Exact figures are not available, but the reality of such a ratio is apparent when it is considered that from one-third to one-half of the fibers composing any spinal nerve-branch distributed entirely to muscle are processes of cells situated in dorsal ganglia. Further, the arrangements of internuncial neurons (Fig. 45) assure still greater conveyance on motor neurons.

Another aspect of the overlapping central distribution of afferent pathways is illustrated by comparing the reflex tension developed (a) on stimulating separately each of two afferent nerves having reflex access to a given muscle and (b) on stimulating them concurrently. It will be found that the reflex tension obtained by the double stimulation is somewhat greater than when only one nerve is stimulated, but it is very much less than the sum of the tensions resulting from stimulation of the nerves separately. The deficit of tension in the concurrent response is called *occlusion,* and its anatomical basis is represented diagrammatically in Fig. 48. Occlusion is a measure of central overlap. Because of overlap a certain fraction of the motor units which can be thrown into action through one afferent path can also be engaged through the other.

Fatigue, Dependence on Blood Supply and Susceptibility to Drugs.—In contrast to peripheral nerves reflex arcs are strikingly susceptible to fatigue. A nerve trunk stimulated at a rate of 40 to 50 times a second will continue to conduct impulses at this rate for hours. In the spinal cat the flexor reflex may fail within thirty seconds when afferent impulses are set up at this rate of stimulation. The fatigue is central, for immediately after failure of the reflex response, stimulation of the motor nerve will evoke a maximal contraction of the muscle.

Another striking difference between peripheral and central conduction is the far greater dependence of the latter on blood supply. Deprivation of oxygen through interruption of blood flow, or reduction of the content of this gas in blood, results in the abolition, within minutes or seconds, of reflex conduction. On the other hand, an approximately normal electric response may be obtained in an excised piece of peripheral nerve trunk kept in cold Ringer's solution three days after its removal from the animal (Forbes). Similarly, central conduction is affected much more rapidly by certain drugs, especially narcotics and anesthetics. A concentration of ether in blood sufficient to put an end to all ordinary spinal reflexes leaves conduction in peripheral axons and across neuromyal junctions unaffected.

The great susceptibility of the central nervous system to fatigue and deprivation of oxygen suggests a high metabolic rate. It has been reported that the heat production of a frog's spinal cord may be 580 to 2324 $\times$ 10^{-6} calories per gram per second at 21° C.[130] We have seen that the heat production of a resting peripheral nerve trunk from a frog is about 70 $\times$ 10^{-6} calories per gram per second and that this low output increases only slightly as a result of maximal activity. Measurements of the oxygen consumption of brain indicate a correspondingly high metabolism of central nervous tissue. The chief seat of this high central metabolism must be the gray matter which has a much more abundant vascular supply than the white matter. The latter is, of course, composed of axons and is therefore quite similar to a peripheral nerve trunk.

That the high metabolic activity of whole neurons is not centered in the cell body, but in the unmyelinated dendritic processes and central axon terminals follows from the interesting observation made by Holmes,[130] that the gasserian ganglion shows an oxygen consumption which is low and of the same order of magnitude as that of peripheral nerve. The sensory ganglia of the spinal and cranial nerves contain cell bodies and nerve fibers, but, so far as is known, no true dendrites or axon terminals.

Inhibition.—Without doubt the most important single fact about central conduction is that many afferent impulses are able to inhibit reflex responses produced by other impulses acting at the same time. Indeed, coordination depends on the inhibition of certain reflexes in order that other more imperative reactions may be carried out without confusion.

It might appear that to bend a joint or to move the eyeball the only muscular action required would be contraction of the muscles which flex the joint or rotate the eyeball, and that antagonistic muscles would merely be passively elongated. When we consider, however, that all the muscles of the body are ordinarily in a condition of slight sustained contraction, and that this "tone," as it is called, tends to be increased when the muscles are passively stretched, then we see that for efficient movement there must be inhibition of the tone of the muscles which oppose those that contract. This *reciprocal inhibition* is a very widespread function throughout the body.[149]

Since the skeletal muscles of vertebrates do not receive inhibitory nerve fibers a reflexly produced diminution or cessation of the contraction of such a muscle can only be the result of a lessening or a cessation of a preexisting discharge in its motor neurons.

Reciprocal inhibition is a most essential factor in the regulation of muscular acts. Thus, in the case of the lateral movement of the eyes, if we cut the third and fourth nerves to one eye, say, the left, the external rectus of that eye will alone be under the control of the nervous system, through the sixth nerve; nevertheless, if we afterward cause the animal to look toward the right, as by holding some object in that direction, it will be found that the left eye as well as the right follows the object. Obviously there must be an inhibition of the tonic discharge of motor impulses to the external rectus muscle of the left eye, an inhibition which is pronounced enough to bring about a movement of the eyeball, and which exactly corresponds in point of time with the contraction of the external rectus of the right eye. This movement, due entirely to the decrease in tone of the external rectus, does not, however, succeed in causing the eye to rotate beyond the midline of the field of vision. This is an instance of a willed reciprocal inhibition; i.e., a reciprocal inhibition brought about by stimuli coming from the motor centers of the cerebral cortex. The same result may be obtained by electric stimulation of the center for eye movements in the cerebral cortex.

Important details concerning the mechanism of central inhibition have been obtained by studying the flexor reflex in a spinal cat or dog which has completely recovered from spinal shock, or in a decerebrate animal. In such preparations the extensor muscles of the knee are maintained in a considerable degree of sustained partial contraction or tonus, which, as we have seen in Chapter X, is the result of asynchronous low frequency discharges over a fraction of the motor neurons. If by denervation and section of tendons we prevent the flexors from acting on the knee joint, nociceptive stimulation of the foot

will cause a visible relaxation of the extensors. If the leg is held properly, this relaxation may be marked enough to cause a definite flexion at the joint under the influence of gravity.

Reciprocal inhibition can also be demonstrated by stimulating the central end of suitable afferent nerves—that is, certain afferent nerves acting on the same groups of neurons will produce a flexion reflex, others an extension reflex; thus, stimulation of the ipsilateral peroneal nerve produces a flexion reflex of the hind limb (excitatory for motor neurons to flexors, inhibitory for motor neurons to extensors), whereas stimulation of the contralateral peroneal nerve produces an extension (inhibitory for motor neurons to flexors, excitatory for motor neurons to extensors) (Fig. 49).

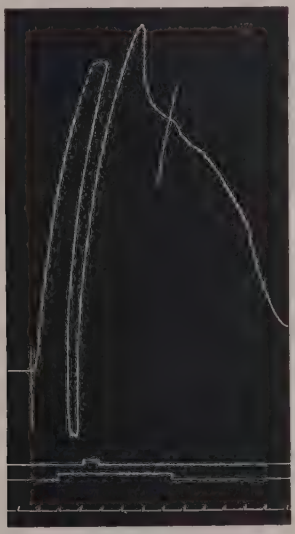

Fig. 49.—Record from myograph connected with the extensor muscle of the knee. During the time marked by the lower signal, the skin of the opposite foot was stimulated, thus causing the crossed extension reflex. While still maintaining this stimulation, faradic shocks were applied to the skin of the foot of the same side (as indicated by the upper signal), with the result that immediate relaxation of the contracted extensor occurred. (From Sherrington.)

Before we can conclude that the two elements in reciprocal inhibition are part and parcel of the same reflex, it must be shown that under whatever conditions the contraction of one group of muscles is brought about, inhibition of the motor neurons supplying their antagonists must also occur and that the responses take place at exactly the same time. If records are made of the movements of the flexors and extensors of the knee in an experiment such as we have just described, it is found that the latent period for the response of agonist and antagonist, whether it be contraction or inhibition exactly coincides. If the strength of the stimulus is gradually increased, the latent period becomes shorter for the inhibitory and active reaction alike, and the synchrony of the reciprocal responses is still preserved. Moreover, the receptive field on the skin from which contraction may be elicited coincides exactly with that for the inhibition of the

antagonistic muscles, as do also the kinds and strengths of stimuli which are effective in each case. The inhibition of the discharge to the antagonists may consequently be considered a part of the same reflex which excites the motor neurons of the agonists. For this reason the reflex mechanism involved is called the *reciprocal innervation of antagonistic muscles.* It is schematically represented in Fig. 50, which gives a simple, perhaps a dangerously simple, picture of the phenomenon of reciprocal inhibition. The diagram is useful only as a means of representing definite experimental results; it should not be regarded as a representation of the intimate mechanism of reciprocal inhibition. The plus and minus signs merely indicate the opposite effects exerted upon the motor neurons of antagonistic flexor and extensor muscles when afferent impulses in a given nerve *enter* the cord. The minus signs should not be regarded as indicating that afferent impulses directly inhibit motor neurons at their synapses, for there is

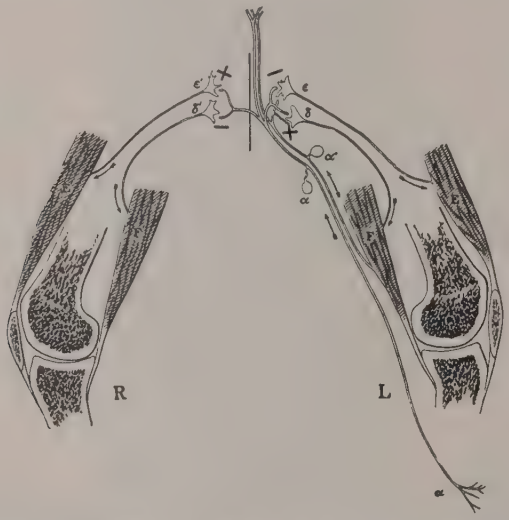

Fig. 50.—Sherrington's schematic representation of the effect of the entry of afferent impulses into the cord upon the motor neurons innervating antagonistic muscles. This effect includes reciprocal inhibition, but it need not be assumed that afferent impulses exert inhibitory effects directly upon motor neurons. The afferent fibers (α) from the skin of the leg and (α') from the flexor muscles of the knee, pass to the spinal cord where each is represented as dividing to supply a branch to a motor neuron (ε) of an extensor muscle (E) and another branch to a motor neuron (δ) of the antagonistic flexor muscle (F). Branches also pass across the median line to similar motor neurons on the opposite side of the cord. Stimulation of α or α' thus causes ipsilateral flexion and contralateral extension, each of which involves reciprocal inhibition. As indicated by the plus and minus signs, the afferent impulses bring about either stimulation or inhibition of the activities of the motor neurons, the determination of the exact effect being a function of an unknown mechanism. (From Sherrington.)

no evidence that they do. On the other hand, these signs may be regarded as indicating that afferent impulses set up central changes which prevent or make more difficult the excitation of these motor neurons.

Since the seat of the inhibition is within the spinal cord, it is to be expected that impulses transmitted from other parts of the nervous system than the particular level of the reflex, will also be able to induce inhibition. In the case of the decerebrate cat this can be demonstrated by stimulation of the lateral columns of the spinal cord; inhibition of the tonic discharges to the extensors

of the elbow joint occurs. Through various tracts of supraspinal origin impulses descend which exercise a marked inhibitory influence on the reflex excitation of the spinal centers for limb extensors.

Central inhibition has many of the same characteristics as central excitation. It can be demonstrated and measured, however, only by its power to reduce or abolish reflex discharge. The effect of an inhibitory volley of afferent impulses may be a subthreshold one. Summation of inhibitory effect can be produced by successive volleys in one or more afferent nerves. The central inhibitory process is quantitatively antagonistic to the excitatory condition which produces reflex discharge; the stronger the latter the greater the number of "inhibitory" afferent impulses per unit time required to abolish it. A single inhibitory volley may set up a central change which will prevent or reduce a reflex discharge for a considerable length of time. For example, the knee jerk, an extensor reflex, is, of course, inhibited by elicitation of the flexor reflex. A single volley of afferent impulses in a suitable ipsilateral nerve may completely inhibit the knee jerk for as long as 1.0-2.0 sec. Fig. 51 shows the impossibility of evoking the jerk during a period of approximately 0.8 sec. following the application of a single electric shock to the central end of the cut hamstring nerve of the same side.

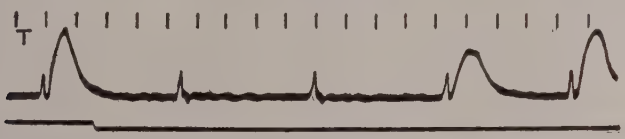

Fig. 51.—Record of knee jerks in a spinal cat showing complete inhibition of the response for a period of 0.8 sec., following application of a single break shock to the ipsilateral hamstring nerve. Signal shows moment of inhibitory stimulus. *T*, time, 0.1 sec. (After Ballif, Fulton and Liddell from Creed, Denny-Brown, Eccles, Liddell, and Sherrington: *Reflex Activity of the Spinal Cord.* The Clarendon Press, Oxford.)

Theories of Central Inhibition.—The phenomenon of central inhibition is without doubt the most poorly understood of all the fundamental characteristics of conduction in brain and spinal cord. In general there has been a tendency on the part of neurophysiologists to attempt to explain this as well as central excitation in terms of the known properties of peripheral nerve fibers.[47, 122, 126, 142]

On this basis the simplest explanation of central inhibition is to assume that motor or other central neurons are innervated by two sets of nerves, comparable to the sympathetic and parasympathetic supplies of the heart, one of which excites and the other inhibits. In the case of the autonomic innervations of visceral effectors such as the heart we know that it is not the character of the impulses transmitted but the physiological specificity of the nerve terminations which determines whether a nerve fiber is excitatory or inhibitory (see Chapter XVI). Therefore in drawing this particular analogy the question is whether there actually are specific inhibitory synapses in the central nervous system. It does not appear that any afferent neurons can be regarded as inhibitory to central neurons in the sense that efferent vagal fibers are inhibitory to the heart, for an afferent volley in any group of dorsal root fibers may produce either reflex excitation or inhibition of motor neurons, depending on the conditions. The evidence thus seems to force the advocate of inhibitory synapses to search for them among internuncial neurons and this requirement of course

presents a different field of investigation. Although there is available no direct evidence of such structures in the central nervous system, it would not be reasonable at the present time to deny their existence.

Because it is founded on positive experimental evidence, one recently developed theory of central inhibition deserves most serious consideration. It too is based on the known properties of peripheral nerve. It will be recalled that when two successive volleys are sent in over fibers of a dorsal root, the first or conditioning volley may facilitate the excitatory effect of the second or testing volley and so cause it to evoke a greater reflex contraction. Now it has been found that the conditioning volley may exert a depressing influence upon the response to the testing volley.[117] This is actually an instance of central inhibition and it is best seen when a large testing volley follows a small conditioning volley which in itself produces only a small motor response. Since the first volley actually produces some excitation, the fibers which carry it cannot be regarded as having inhibitory endings, yet these very same impulses depress the motor response to the second volley. That the mechanism underlying this inhibition is bound up with changes of excitability in internuncial neurons was first established by Hughes and Gasser (see Gasser,[47] pages 194-197) in their study of the cord potentials which have been described above. It was found that when the reflex response to the second volley was depressed by the first, the cord potentials provoked by the second consisted in a much smaller and shorter negative wave and a much more conspicuous positive wave than when this same stimulus set up an unconditioned afferent volley of the same magnitude. Since the negative cord potential denotes the passage of impulses in internuncials and the positive potential signifies subnormality in internuncials it was concluded that the depression of the response to the second volley was due to the raised threshold of internuncial neurons. Later Hughes, McCouch and Stewart[131] were able to show by synchronous recording of the cord potentials and the tensions of the reflexly responding muscles that the extent of the inhibition of a reflex contraction produced by an incoming volley is roughly proportional to the depth of cord positivity obtaining at the time. Thus there is excellent evidence that certain examples of reflex inhibition can be correlated with signs of unresponsiveness in internuncial neurons. How far this undoubted correspondence may be used in explaining inhibition remains to be determined.

Two difficulties stand in the way of complete acceptance of the view that reflex inhibition is due to the blocking of pathways between afferent and efferent neurons by development of subnormality in internuncial neurons. First, there is the fact that since subnormality in a neuron can arise only as the result of the discharge of an impulse by a cell, the depth of positive cord potentials correlated with marked reflex inhibition indicates considerable previous transmission of impulses, and this raises the question why such a source of excitation of motor neurons does not reveal itself in some reflex contraction prior to the period of reflex inhibition. A second difficulty which must be faced by this interpretation of the nature of inhibition is the great length of the reflex depression which can be evoked by a single afferent volley. In some of the experiments of Ballif, Fulton and Liddell, from whose report Fig. 51 was taken, one large ipsilateral volley completely inhibited the knee jerk for as long as 1-2 sec. (i.e., over 1,000 msec.). No positive cord potential of this duration has ever been recorded. In spite of these and other objections, the

concept of central inhibition as due to the development of subnormality and summation of subnormality in internuncial neurons is the most definite explanation of this puzzling phenomenon which has yet been advanced. It is superior to all other theories in that it is based on a positive correlation of two groups of experimental facts.

There is also evidence that subnormality in motor neurons can cause a state of unresponsiveness in these elements which is very like inhibition.[47] When an afferent volley evokes a discharge over motor neurons which are responding to some continuous source of stimulation, the discharge is followed by a period during which no motor impulses are sent out. In other words, the intercurrent elicitation of the reflex leaves the motor neurons unresponsive to the continuous stimulation for a short time. This *silent period*, as it is called, is conspicuous in electromyograms recorded from the muscle involved. If action potentials are taken from a knee extensor of a human being during moderate voluntary extension of the leg, the record shows a series of small irregular excursions. When the patellar tendon is tapped, the brief reflex tetanus which is the knee jerk is signalled by a large brief potential wave after which the record shows a complete absence of any motor discharge for a period of 60 msec. or longer. At the end of this silent period the small potentials signalling voluntary contraction begin again. Experiments on animals have yielded more precise information concerning the genesis of the silent period. An example is found in the work of Hoff, Hoff and Sheehan[129] who studied the effect of an afferent volley on the slow rhythmic tonic discharge of nerve impulses over single fibers to the soleus muscle. The interpolation of an afferent volley was followed by a pause in the rhythmic discharge which lasted longer the closer the added response was to the last preceding impulse. Since an interpolated antidromic volley had exactly the same effect, it can be concluded that the silent period depends on a change in the motor neuron itself, and this change can be nothing other than the development of additional subnormality as a result of added activity. The time course of the silent period corresponds closely with the period of subnormality in motor neurons which follows a single response. If the silent period is regarded as a typical example of central inhibition, the parallel between inhibition and subnormality is here most apparent. But again we are confronted with the fact that the unresponsiveness follows previous activity whereas there is evidence that motor neurons can be rendered unresponsive by reflex inhibition when they have not shown previous activity.

CONDUCTION THROUGH SYMPATHETIC GANGLIA

Many of the difficulties which beset the investigation of the process of synaptic transmission in brain and spinal cord are due to the anatomical complexities of the central nervous system. To avoid these a number of physiologists have used certain of the outlying ganglia of the sympathetic system, especially the superior cervical and the stellate ganglia, which are easily approached and have central and peripheral connections that can be stimulated or lead from without much difficulty. The sympathetic ganglia contain the cell bodies of postganglionic neurons which innervate various visceral effectors. They receive impulses from the fibers of preganglionic neurons whose cell bodies lie within the gray matter of the spinal cord (see Fig. 64, page 168). In any ganglion the only synapses are those which connect preganglionic terminations with the postganglionic neurons. There are no internuncial neurons and in this respect the ganglion differs strikingly from the central nervous system. It is well established that each preganglionic fiber branches to make synaptic connections with a number of postganglionic neurons and that each ganglion cell receives several or many terminations. Thus the anatomical arrangements assure overlap and convergence and provide for spatial summation.

Characteristics of Synaptic Transmission in Ganglia.—It was shown by Bishop and Heinbecker and later confirmed by others (see Eccles[85]) that con-

duction through the synapses of a ganglion is strictly unidirectional; antidromic impulses in postganglionic fibers never set up impulses in preganglionic fibers. There is a short synaptic delay of about 2.5 to 5.0 msec. which, like that of central motor neurons, varies only within narrow limits.[119]

The most accurate analyses of the characteristics of synaptic transmission within ganglia have been made by studying the action potentials occurring in postganglionic fibers when various stimuli are applied to preganglionic fibers. For example, Bronk and his collaborators[110] have recorded postganglionic impulses set up in the inferior cardiac nerve when preganglionic impulses are sent into the stellate ganglion; the several central connections or roots of this ganglion permit an easy study of the effects of stimulation of different preganglionic pathways and different numbers of presynaptic fibers. Using the height of the spike potential of the postganglionic nerve trunk as an index of the number of activated ganglion cells, it was shown that the responses to preganglionic volleys in fibers of one root are greatly augmented by concurrent repetitive stimulation of a second root. This is a clear example of spatial summation and it emphasizes the multiple innervation of the ganglion cells. Obviously impulses in fibers of the second preganglionic root activated many cells in the subliminal fringe of the pool of neurons affected by the impulses in the fibers of the first root. Previously Eccles[85] had found evidence of convergence, occlusion, and subliminal fringe in the superior cervical ganglion.

By taking records from single postganglionic fibers, Bronk, Tower, Solandt and Larrabee[111] showed that one synchronized preganglionic volley evokes only one impulse in each of the ganglion cells which respond; there is no repetitive discharge (after-discharge). The same is true for slowly recurring volleys, but when the preganglionic nerve is stimulated at frequencies of 50 or more per second, individual ganglion cells may continue to discharge for some minutes after cessation of the stimuli. This is a definite case of after-discharge, but Bronk[110] points out that it is produced only by frequencies of preganglionic impulses which are greater than any observed coming from the centers (maximum about 20 per sec.) and therefore "must be considered a clue to the nature of synaptic processes and not a phenomenon associated with a naturally activated ganglion." Further evidence for the persistence of the excitation developed in a ganglion by a presynaptic impulse was secured when it was shown that trains of uniform preganglionic volleys at frequencies of only 3 to 10 per second recruit into action more and more ganglion cells.[110] This shows that the subliminal effects produced by each of the volleys persist long enough to summate ultimately to a threshold level, and it suggests the occurrence of true temporal summation. By another method Eccles had previously found that some ganglion cells have an increased excitability for 200 msec. after a preganglionic volley. Transmission through a ganglion is without benefit of internuncial activity. Here, therefore, summation, after-discharge, recruitment, and other signs of the lasting excitatory effect of an afferent (preganglionic) volley cannot be explained by internuncial bombardment. One is confronted with the question whether ganglionic transmission involves some agent or agents which are absent or less prominent in central synaptic transmission.

The growth in effectiveness of preganglionic impulses occurring in succession could be due to changes in the excitability of the ganglion cells. Eccles,[85, 119] by using the antidromic shock technique (see page 100) showed that the backfiring of a volley in post-

ganglionic impulses reduced the number of cells activated by a testing preganglionic volley for more than 0.5 sec. and Bronk[110] has demonstrated that the postganglionic response to a preganglionic volley may be decreased for several minutes when a train of antidromic impulses is used. Since this same depression of the synaptic excitability of the ganglion cells (sometimes called inhibition) must follow their activation by presynaptic impulses, we may ask why it is that a succession of such stimuli evokes greater rather than less activity. Whatever the explanation, the facts show that "the train of impulses that initiates activity in the ganglion cells and thus causes a subsequent lowering of their excitability also develops conditions which increase the effectiveness of succeeding presynaptic impulses" (Bronk[110]). Eccles[85] has attempted to follow the changes in the excitability of ganglion cells by recording the slow potential waves which are produced at a ganglion by a presynaptic volley and which in sign and sequence closely resemble both the after-potentials of peripheral nerve and the potentials of the spinal cord. He reported that the ganglion cells have a lower threshold to a preganglionic volley during the negative potential and a higher one during the positive phase. The ganglion thus appears to provide another close correlation between the after-potential cycle and the excitability cycle of postsynaptic neurons. Eccles, however, has found that the increased excitability concurrent with the negative potential may be produced by a subliminal volley. Rosenblueth and Simeone[148] maintain that the excitability of the ganglion cells may be quite independent of the negative and positive potentials. Their view has reference to a particular theory of synaptic transmission and we shall return to this later.

Theories of the Mechanism of Ganglionic Synaptic Transmission.—The main characteristics of ganglionic transmission have been presented. It remains to inquire into the mechanism of this example of synaptic transmission. Experimental results have led to the same two opposed theories which have been discussed in connection with transmission of excitation at the neuromyal junction (Chapter VIII). The evidence bearing upon this problem can be only briefly summarized here. The interested reader is referred to the discussions and reviews by Dale,[82] Forbes,[123] Eccles,[85, 120] Brown,[112] Cannon[80] and Bronk.[110]

The *theory of chemical mediation* had its origin in the work of Dale and his collaborators which began in 1934. It is based chiefly on: (1) evidence that acetylcholine is liberated in ganglia by preganglionic impulses; (2) the elicitation of discharges over postganglionic neurons by perfusing low concentrations of acetylcholine through a ganglion; and (3) potentiation of the effects of submaximal preganglionic stimulation by perfusing the ganglion with weak concentrations of eserine, a substance which, it will be recalled, protects acetylcholine against destruction by cholinesterase. Such experimental results soon led to rather wide acceptance of the view that presynaptic impulses liberate in the ganglion small amounts of acetylcholine which in turn excite the ganglionic neurons. This theory represents acetylcholine as the transmitter of excitation at the synapses. Following the initial work additional results lent further support to the theory. The association of liberation of acetylcholine with forward conduction in a ganglion was emphasized by the report that antidromic impulses in postganglionic fibers do not cause the liberation of acetylcholine in the ganglion. It was also reported that sympathetic ganglia contain a higher proportion of acetylcholine than most other organs.

Serious criticisms of the chemical theory have been put forward. Eccles[85, 120] has used the argument that since a persisting concentration of acetylcholine causes sustained firing of impulses from a ganglion the hypothesis of mediation by this substance cannot well account for the fact that a single preganglionic volley causes the discharge of only one postganglionic volley. He has pointed out that the process underlying synaptic transmission must develop and decay within a period not longer than 6 msec. and raised the question whether acetylcholine can appear and disappear during such a short interval.

In the case of neuromuscular transmission, where the time factor is even shorter, this objection has been met by evidence that cholinesterase occurs in sufficient concentration at the neuromyal junction to cause the amounts of acetylcholine to disappear within the refractory period. It is therefore significant that Brücke[115] has found a concentration of this enzyme in the superior cervical ganglion which is about three times greater than that in the nonsynaptic nodose ganglion of the vagus or in the cervical sympathetic trunk. Lorente de Nó,[141] in a repetition of the original perfusion experiments done in Dale's laboratory, found no constant relationship between preganglionic stimulation and the appearance of acetylcholine in perfusates, indicated that the alleged mediator appears in greatest amounts when the ganglion cells are injured, and obtained evidence not only that the firing of antidromic impulses into the ganglion leads to its production there but also that it is released in the nonsynaptic vagus ganglion on appropriate stimulation. MacIntosh[144] in turn has failed to confirm the observations of Lorente de Nó and there the matter stands. Such conflicting reports can be appraised only by the way in which they fit into the general pattern of evidence bearing on the problem of ganglionic transmission.

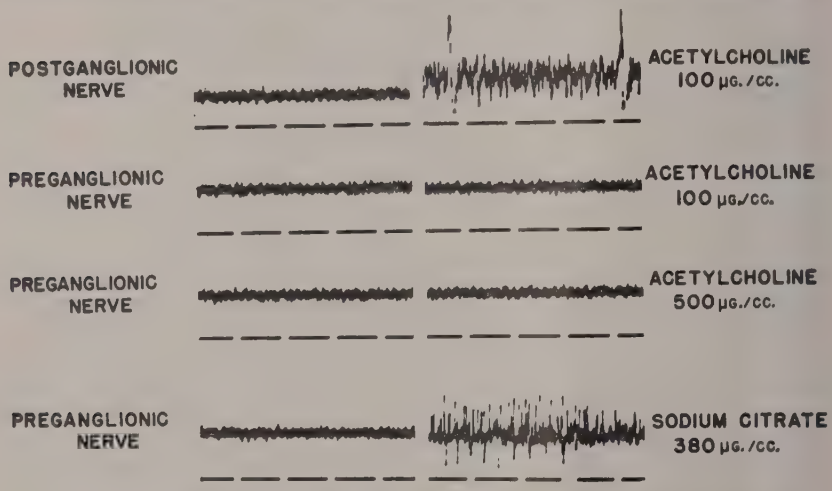

Fig. 52.—The records in the right hand column show the responses (action potentials) in preganglionic and postganglionic nerves to perfusion of the ganglion with acetylcholine or sodium citrate in the concentrations indicated. Controls with Ringer's fluid in left hand column. Lowermost record: time intervals of 0.1 sec. (From Bronk: J. Neurophysiol. 2: 380, 1939.)

Very strong circumstantial evidence supports the view that acetylcholine either is the transmitter of excitation in sympathetic ganglia or plays an important part in the process of transmission. It was originally shown by Feldberg and Gaddum (1934) that perfusion of a low concentration of acetylcholine through a ganglion increases the number of cells responding to a preganglionic volley and this has been beautifully confirmed by Bronk and his collaborators. Thus the substance appears to facilitate excitation in the subliminal fringe and it may be responsible for the enduring effects of a preganglionic volley. Bronk[110] has also provided us with the best proof that the action of acetylcholine on ganglion cells is specific. He showed that when acetylcholine in a concentration of 100 μg. per ml. of perfusion fluid caused a vigorous discharge of impulses in postganglionic fibers, the preganglionic fibers remained silent even when the concentration of the drug was raised fivefold (Fig. 52). At the same time the excitability of the preganglionic elements under the conditions of the

experiment was demonstrated by their response to sodium citrate in the perfusing fluid; this substance causes continued excitation of nerve cells and fibers in general.

There is evidence that the chemical theory must take into account other substances than acetylcholine. Brown and Feldberg[113] found that potassium, like acetylcholine, increases the responses of the superior cervical ganglion to single submaximal preganglionic volleys and causes denervated (preganglionic fibers degenerated) as well as normal ganglia to discharge impulses. Potassium also causes the liberation of acetylcholine from innervated ganglia; it liberates insignificant amounts in denervated ganglia. That it has a much less specific action than acetylcholine is shown by two facts: (1) it excites preganglionic as well as postsynaptic neurons, and (2) after application of nicotine, which blocks normal transmission in autonomic ganglia, it does not excite the ganglion cells whereas acetylcholine does.[114] Bronk[110] has shown that the concentrations of potassium and calcium modify the discharges produced by a given amount of acetylcholine in the perfusion fluid. The frequency of impulses in a single postganglionic fiber is increased by raising the potassium concentration or lowering the calcium level; it is reduced by a decrease in potassium or an increase in calcium. If acetylcholine is an essential factor in transmission, its activity must be greatly modified by ionic changes in the environment of the ganglion cells.

The *electrical theory* of transmission, as applied to the synapses of sympathetic ganglia, takes essentially the same form which was outlined in the discussion of neuromuscular transmission (Chapter VIII). It postulates that ganglionic cells are stimulated directly by the action currents of impulses arriving at the presynaptic endings. If we may characterize the evidence for the chemical theory as strongly circumstantial, that supporting the electrical theory is even less direct. One of the foremost arguments which has been used for the electrical theory in its general application is that the time course of the excitatory process in the postsynaptic or postjunctional cell is about the same as the time course of the action potential in the presynaptic or prejunctional element. While this parallelism may be accepted as a fact, it does not explain the enduring effects of preganglionic volleys described above, effects which of course cannot be attributed to internuncial bombardment and which may be due to a lowering of the excitability of ganglion cells or to some alteration in the effectiveness of preganglionic impulses at the presynaptic terminations. Eccles[85] has sought to support the electrical theory by correlating the slow ganglionic potentials with changes in the excitability of the ganglion cells. The first or negative wave is associated with increased excitability to presynaptic impulses and the second or positive phase with a raised threshold to these stimuli. Since this correlation agrees with the changes in excitability to electrical stimuli shown by peripheral nerve during the negative and positive after-potentials, the assumption is made that the presynaptic endings stimulate through the agency of action currents. But this double correlation lost any strength it may have possessed as an exclusive argument for the electrical theory when it was shown by Bronk and his associates[110] that the threshold of the ganglion cells to stimulation by acetylcholine is lowered during the course of the negative ganglion potential and raised throughout the positive potential. Since these changes in the chemical excitability of the cells are the same when the after-potentials develop as a result of antidromic volleys, they must be due

to previous activity in the postganglionic neurons. Results which do not appear to be explicable on the basis of the electrical theory but are, for the most part, understandable in terms of the chemical theory were secured by Cannon and Rosenblueth[116] and Lanari and Rosenblueth[132] when they showed that with rapidly repeated stimulation of preganglionic fibers transmission of excitation in the eserinized superior cervical ganglion (as judged by the contraction of the nictitating membrane of the cat) passes through the same five stages which characterize neuromuscular transmission (see page 63).

A *dualistic theory* of ganglionic transmission, in which the action current and acetylcholine somehow cooperate in exciting the ganglion cells and in producing the other changes we have described, is possible. The two theories may not be mutually exclusive. Bronk's studies have led him to prefer, at least for the time being, a *pluralistic theory*.[110] He emphasizes particularly the concept that the properties of both the preganglionic terminations and the postsynaptic cells are continually changing in accordance with their changing environment and their previous activity. The essence of this view is that at any given instant any one of several possible changes may be the factor which is the immediate cause of a postsynaptic discharge.

THE NATURE OF CENTRAL SYNAPTIC TRANSMISSION

A discussion of the intimate nature of synaptic transmission in the central nervous system must be based primarily on the known characteristics of central conduction. But it is reasonable to take also into consideration the available facts and theories concerning transmission at synapses in sympathetic ganglia and at neuromyal junctions. Indeed there is, as we have seen, good reason to ask whether after all there are any fundamental differences between conduction in nerve fibers and conduction across interneuronal or neuromyal junctions. The only positive indication that we have of a real difference is the evidence which favors the view that mediation of excitation is chemical at the ganglionic and neuromyal junctions.

In considering the mechanism of synaptic transmission we must keep clearly in mind the distinction which has been drawn between (1) the subliminal and liminal excitation of central neurons by presynaptic impulses and (2) the changes in excitability of central neurons which follow the discharge of one or more impulses. A further point is the possible occurrence of a delayed lowering of threshold following subliminal presynaptic excitation. Repetitive stimulation by internuncial bombardment constitutes a phenomenon peculiar to the central nervous system, but it in no way transcends these more fundamental processes. We may now review the excitatory reactions which take place in the synaptic region and seek to define them more rigorously, for all interpretations of synaptic transmission must be based on an understanding of these phenomena.

Detonator Action and Central Excitatory State.—The phenomena of summation and facilitation show that a subliminal excitatory condition produced by one volley of presynaptic impulses develops rapidly and then subsides progressively until, after a certain interval, not enough of it is left to render a second impinging volley an effective stimulus. This enduring central condition was termed by Sherrington and his co-workers the "central excitatory state" *(c.e.s.)* without any implications as to its precise nature. It was assumed that

on reaching a central neuron converging impulses are transformed into so much *c.e.s.* When this becomes sufficiently intense the neuron discharges an impulse. Thus the central excitatory state is graded and cumulative, and it was likened to the local excitatory process which sets up an all-or-none conducted response in nerve or muscle. Certain results indicated that in the case of spinal reflex arcs *c.e.s.* lasts as long as 10 to 20 msec. but as noted above Lorente de Nó[138] has shown that the maximum interval for spatial summation at the synapses of the eye muscle nuclei is not longer than 0.5 msec., a figure which corresponds closely to the minimal synaptic delay. It is this brief period which actually seems to correspond to the local excitatory process set up in a peripheral nerve by a stimulating current.

Later Eccles,[85] as a result of his studies of ganglionic transmission, came to use the term *c.e.s.* in an entirely different sense and it is so used in much of the current literature. He calls the brief excitatory effect of presynaptic impulses the *detonator action.* The corresponding change in the neuron is called the *detonator response;* when this reaches threshold value the typically explosive discharge of an impulse occurs. Eccles reserved *central excitatory state* (and its abbreviated form *c.e.s.*) to describe a later or second period of lowered threshold which develops after dissipation of the detonator response. Lorente de Nó[142] has referred to this as a *second phase of summation.* According to Eccles it occurs in subliminally stimulated neurons as well as in cells which have responded by discharging an impulse. It differs from the detonator response by surviving the refractory period and in never giving rise to an impulse. Its only effect is to lower the threshold at which impulses are set up by the detonator response. In the cells of the superior cervical ganglion it keeps the threshold lowered to preganglionic impulses for as long as 50-200 msec., and it is associated with a slow negative potential. Since it is produced in ganglion cells of the subliminal fringe in which no impulse is set up, it differs from the supernormal phase of nerve and the associated negative after-potential which are observed only as sequels to the conduction of an impulse.

The concept of *c.e.s.* as a long lasting increase in excitability which in itself cannot set up an impulse and which occurs in response to subliminal as well as liminal synaptic excitation is based almost wholly on evidence obtained in studies of sympathetic ganglia. The importance of the question whether it occurs in central neurons is stated clearly in the following quotation from Lorente de Nó:[142] "If nerve impulses arriving at synapses should develop only detonator actions which are no longer in duration than the absolutely refractory period of presynaptic fibers, then temporal summation of impulses arriving in succession through the same fiber would be impossible, and in the nervous system no other type of summation could exist than the spatial summation of impulses arriving simultaneously or within a short interval of time through different synapses. But if subliminal impulses should produce a second phase of lowered threshold, then temporal summation of impulses conducted in succession by the same fiber would occur." But no conclusive evidence has been secured that *c.e.s.* in Eccles' sense develops in central neurons. Lorente de Nó has been unable to demonstrate in a convincing manner a second phase of lowered threshold in subliminally stimulated ocular motor neurons, but he points out that this does not exclude its development and "proves only that the lowering of threshold due to such a process is small in relation to the change in threshold produced by alteration of the intensity of the internuncial bombardment, and

therefore cannot be demonstrated if a variation in the strength of the internuncial bombardment takes place.'' Indeed the occurrence of internuncial bombardment at almost all central neurons when they are activated reflexly or by impulses from a distance makes it most difficult to solve this problem experimentally. Certainly much of the activity of central neurons can be explained in terms of the activity of chains of neurons and the detonator actions of impulses arriving at presynaptic endings.

The Synaptic Transmitter.—The narrow time limits of the synaptic delays at motor neurons (0.5-0.9 msec. for oculomotor neurons;[138] 0.5-1.0 msec. at anterior horn cells[147]) show that the transmitter of excitation acts within that brief interval of time. According to Lorente de Nó the length of the period during which two groups of impulses arriving at an oculomotor neuron may produce spatial summation is not longer than 0.5 msec. This maximum summation interval is therefore equal to the lower limit of the synaptic delay. This must be the duration of the detonator action of presynaptic impulses. Now there is good reason for believing that the major portion of the spike potential which accompanies impulses travelling in fibers of the posterior longitudinal bundle lasts about 0.5 msec.[138] This consideration has lent considerable support to the view that presynaptic impulses stimulate nerve cells across synapses through the agency of their action currents.

On this hypothesis the true synaptic delay is not due to the actual transmission, for the passage of the current is practically instantaneous. On the other hand, if the current has a detonator action, it would exert its effect over at least a portion of its duration. Also the detonator response may lag behind the exciting current. It has been suggested by Eccles[85] that brief detonator action takes place under individual synaptic knobs and spreads decrementally for a small distance over the dendrite or cell body; summation would then occur when adjacent synapses are excited within the very short intervals during which these decrementally spreading excitations last. On this basis synaptic delay may be explained, in part at least, by the time necessary for this spread and summation of the detonator responses set up under neighboring synaptic knobs. This idea is in accord with Lorente de Nó's evidence that spatial summation depends upon the simultaneous arrival of impulses at a sufficient number of adjacent synapses on each neuron (see page 99).

The electrical theory of central synaptic transmission received much bolstering when Lorente de Nó[135] demonstrated that the soma of the central neuron (cell body and dendrites) is electrically excitable and that a subliminal afferent volley and a subliminal induction shock applied directly to the motor neurons can sum to produce threshold excitation. From this it has been argued that the two exciting agents must be alike and therefore the action current is the synaptic transmitter.

The hypothesis of chemical mediation of excitation at the synapses of the central nervous system is, as Eccles[85] has pointed out, almost entirely based on an extrapolation of the chemical theory of transmission in sympathetic ganglia. There is little evidence to indicate that the effects of acetylcholine on the central nervous system are similar to those which it exerts in the ganglia. Yet the concentration of cholinesterase appears to be always greater in gray matter than in white matter,[120] and this fact may have some significance. In a recent discussion of this question Forbes[123] has pertinently remarked that ''if it is finally established that intercellular transmission is chemically mediated in such widely different systems as the neuromuscular junctions of smooth and striated muscle and the synapses of the ganglia, the operation of a wholly different mechanism in the histologically similar synapses of the central gray

matter would be a most surprising anomaly." Certainly at present there is no compelling reason to suppose that the hypothesis of transmission by acetylcholine or some similar substance cannot be extended to the synapses of the central nervous system. It may also be mentioned that there is no reason why a chemical substance liberated at synaptic terminations should not lower the threshold of central neurons and Forbes therefore points out that the demonstrated ability of a subliminal presynaptic volley to sum with a subliminal electrical stimulus applied directly to motor neurons is not conclusive proof of the identical nature of the two excitatory agents. Indeed, as we have seen, acetylcholine definitely lowers the threshold of ganglion cells to a subliminal preganglionic volley; it facilitates excitation in the subliminal fringe and could therefore be regarded as setting up *c.e.s.* or the equivalent of a second phase of summation. It is also apparent that this substance has a detonator action on ganglion cells, for it causes discharges from denervated ganglia.

In the light of our present knowledge it would be premature to adopt any fixed theory of synaptic transmission. Decision must be delayed. We need to know a great deal more about the ways in which the properties of the elements on the two sides of the synapse vary under the normal condition of a continued arrival of impulses at varying frequencies. The final solution may present us with a picture in which the electrical and chemical changes, with which we are now so concerned, appear as perhaps the more obvious features of an integrated mechanism. Whatever that mechanism may be, the results obtained by Bronk in his studies of ganglionic transmission indicate that it is surely one which is susceptible to disturbances in local metabolism and to changes in blood supply. Since transmission at synapses lies at the basis of all central nervous activity, it is not too much to say that until this problem is solved we will not have any fundamental understanding of the causes of nervous and mental disease.

CHAPTER XIII

THE INTEGRATION OF REFLEX ACTIONS

THE INTEGRATION OF ACTION WITHIN THE REFLEX ARC

The grading of a reflex is regulated by the interaction of the excitatory and inhibitory effects of different afferent impulses. This is the quantitative side of reflex activity. It remains to give some further explanation of the qualitative feature of individual reflexes, of the fact that each is a response in which a group of muscles act in a coordinated way so as to accomplish some purpose which is related to the excitatory stimulus. The characteristic purposiveness of a reflex is the result of a number of factors which operate at different parts of the arc.

The Action of the Receptors.—For purposes of analysis the physiologist frequently elicits reflexes by stimulation of bared nerve trunks. This practice is justifiable only when, in appraising the result, it is kept in mind that the afferent fibers which are thus stimulated connect with a variety of receptors and subserve different reflex functions. Under normal conditions reflex acts are initiated by the stimulation of receptors. Because each receptor is specialized to respond more readily to one quality of stimulus than to any other (page 66), each reflex arc is brought into action only by stimuli of an appropriate sort. The selective excitability of the receptors of the different reflex arcs consequently enables the organism to respond in different ways to stimuli of different kinds when they are applied to the same receptive surface area. As an example we may consider the reactions which may result from stimulation of the foot of a spinal cat or dog. Pressure against the undersurface of the paw elicits the extensor thrust. This response cannot be called forth by any other form of stimulus. As we have seen, it is an item of behavior of significance in supporting the weight of the body at the end of each step. If a harmful stimulus is applied to the same part of the foot, the response is of a totally different character, consisting of a flexion of the joints of the limb. It serves to protect the foot from harm and fulfills a purpose entirely different from that of the extensor thrust. The receptors for these two reflexes have their thresholds lowered each to a particular form of stimulation, and the nature of the response is such that the leg moves in a way which is appropriate to the conditions under which stimulation occurs. The kind of reflex set up is thus determined by the kind of receptor stimulated, but the destiny of the nerve impulses discharged by the receptor and the quantitative characteristics of the reflex response are determined by the peculiarities of central conduction which have been described in the preceding chapter.

Independent Rhythm.—All reflex responses are rhythmic in the sense that activity in motor nerve fibers must be discontinuous. As we have seen, the rhythm of discharge is largely imposed by the reflex center. Many reflexes, however, are rhythmically occurring muscular acts. Examples are the scratch reflex and the stepping which may be evoked in a spinal cat or dog. In these

cases the rhythm of the act is also imposed by the reflex center, being independent of the rhythm of the stimulus. In the scratch reflex no matter how frequently we apply suitable stimuli to the sensory surface, the rhythm of the response of the limb is always the same. The phasing of the act is thus not related to the changes in the periphery. If a scratch movement is elicited by stimulation of a point A in the proper skin area, the rhythm of response which it calls forth is not in any way altered by the application of a second stimulus at B at some distance from A and having a different frequency. The ability of central mechanisms to control the rhythm of an act is excellently demonstrated by the fact that stepping movements may occur in the deafferented limbs of spinal animals and that both stepping and scratching are favored by the first stages of asphyxia and narcosis.

The Principle of Reciprocal Innervation.—The significance of this factor in the integration of a reflex act has already been dealt with in the discussion of central inhibition. It is necessary, however, to define more precisely the conditions under which antagonistic muscles act reciprocally, for certain reactions are carried out without benefit of this principle. Experiment has shown that in the execution of phasic movements increase in tension never occurs concurrently in antagonistic muscles; nor does decrease in tension proceed in this manner. The principle does not imply that two antagonists cannot be in a state of contraction at the same time, for the inhibited muscle may not be completely relaxed. It is important to realize that there is at least one significant exception to the general rule that increase in contraction does not proceed concurrently in antagonistic muscles. This exception—and there may be others—is the positive supporting reaction, a nonphasic postural response (see page 139) which fixes the limb as a rigid pillar for the support of the body during standing. In this the extensors and flexors, abductors and adductors of hip and knee, shoulder and elbow, go into action simultaneously and maintain contraction concurrently. Here the exciting stimulus is the stretch of the muscles which ventroflex the distal joints. The afferent impulses set up by these proprioceptors apparently act only as excitatory stimuli at their central destinations.

The principle of reciprocal innervation may concern itself with only two opposed muscles, as in the case of simple eye movements, or it may operate through a large group of such muscles. In the flexor reflex of the hind leg about a dozen muscles contract and very nearly the same number undergo reciprocal relaxation. The muscles of each of these two groups are synergic, i.e., they act in the same direction mechanically at the same joint or at two neighboring joints. The reflex act set up by afferent impulses from a limited group of receptors may not be confined to the antagonistic muscles of the joints of one limb. In response to a nociceptive stimulus applied to one hind foot ipsilateral flexion is combined with contralateral extension. This is a case of double reciprocal innervation, for the principle operates equally in the reactions of both legs. The principle even governs such extensive reflex acts as the development and maintenance of any one of the reflex figures shown in Fig. 42. In all parts of the reflex figure reciprocal inhibition takes place, as can be demonstrated by studying the behavior of each reacting muscle. In each limb and at the neck it is found that the tone of those muscles which oppose the assumption of the reflex figure is lessened.

Graded Synaptic Resistance.—The synapses in which the collaterals of any group of afferent neurons terminate differ considerably in the resistance which they offer to the passage of nerve impulses. Some synapses are passed as a result of minimal summation, others are normally resistant to an almost unlimited sequence of afferent impulses. The wealth of the potential connections of any afferent fiber and the normal resistance of the majority of these are demonstrated most dramatically by the action of strychnine. After the administration of this drug, a sensory stimulus which excites only a few afferent fibers will produce reflex contractions, convulsive in nature, in nearly every muscle in the body. The characteristic action of this substance is to break down the normal synaptic resistance.

The normal graded resistance of the synaptic pathways of the central nervous system may be due either to a difference in the amount of summation required for excitation at different synapses or to varying degrees of convergence of groups of afferent impulses at their different central destinations. Probably both of these factors operate. The necessity of summation in the production of any normal reflex discharge is itself of great importance in regulating and integrating reflex activity. This can readily be appreciated when it is realized that the organism is constantly in receipt of many unimportant stimuli which are, nevertheless, above the threshold of a few receptors.

By applying graded stimuli to a single afferent path one may grade the extensiveness as well as the intensiveness of the reflex produced. This is well illustrated in the development of a reflex figure by nociceptive stimulation of one hind foot of a decerebrate cat. In applying stimuli of increasing strengths, first the ankle alone is flexed, then the knee, and finally the hip. The response then spreads to include the extension of the contralateral hindleg and finally involves the forelegs also. The mechanism which determines the course of this march of the reflex figure is the graded resistance of the synapses. It may be reemphasized, however, that as the reflex spreads to each new joint the inhibition of the antagonists occurs coincidently with the contraction of the active muscles, and the resistance of the synapses lying in the path to the antagonistic muscle groups must be equal.

Sherrington[149] has laid down the following rules for the spread of short spinal reflexes, as the components of a reflex figure which involve only a few spinal segments may be designated:

1. The degree of reflex spinal intimacy between afferent and efferent spinal roots varies directly as their segmental proximity.

2. For each afferent root there exists in immediate proximity to its own place of entrance in the cord, e.g., in its own segment a reflex motor path of as low a threshold and of as high potency as any open to it anywhere.

3. Motor mechanisms lying in the same region of the cord are unequally accessible to the local afferent channels, if judged by pressor effects, i.e., the production of contraction. This rule breaks down, however, when it is considered that an afferent path may produce inhibition in many of the motor mechanisms to which it has access.

4. The groups of motor nerve cells contemporaneously discharged by spinal reflex action innervate synergic and not anergic muscles. As a consequence the muscular contractions are harmonious with one another (reciprocal inhibition).

5. The spinal reflex movement elicitable in and from any one spinal region will exhibit much uniformity despite considerable variety of the locus of incidence of the exciting stimulus.

The spread of long spinal reflexes, which are parts of a reflex figure involving many segments of the cord, is too inconstant in a single reflex figure and varies too greatly in different figures to permit any definite rules to be laid down.

THE INTEGRATION OF SIMULTANEOUS AND SUCCESSIVE REFLEXES

The Principle of the Final Common Path

A single simple reflex acting independently of the rest of the central nervous system does not really occur. It is, as Sherrington has observed, a convenient abstraction. We have seen that an afferent impulse on entering the spinal cord spreads so as to involve a large variety of motor neurons. Each of these unit paths may, however, be excited through other afferent fibers arriving either from other receptors or from higher nerve centers. Any motor neuron on which we focus our attention is therefore occupied at different times by impulses set up by excitations of diverse origins. Hence it is appropriately called the *final common path,* and its activity at any moment must be a function of the various afferent impulses that are transmitted to it through its many synapses. That each motor neuron must be at the service of several afferent neurons follows, on statistical grounds, from the fact that afferent neurons considerably outnumber efferent neurons. Reflex connections involve usually, probably always, one or more internuncial neurons, and these may act as a common path connecting several receptors with a common motor mechanism.

The various reflexes which share the final common path leading to a single group of muscles may cause these muscles to respond (1) in some definite way —as in the maintained contraction of the flexion reflex; (2) in some different way, as in the rhythmic response of the scratch reflex; or (3) inhibition may be produced so that no contraction can be brought about. Reflexes belonging to any one of these groups are *allied reflexes,* because they have a common effect on the motor mechanism. Reflexes belonging to different groups, which consequently affect the final common path to different purposes are *antagonistic reflexes.* Integration in reflex activity depends on the consequences which follow when allied or antagonistic reflexes act upon the final common path, either simultaneously or in rapid succession.[149]

The Integration of Allied Reflexes

Simultaneous Combination.—The scratch reflex is well adapted for the study of this subject since the skin area from which this reflex can be elicited is very widespread. The type of reflex produced from any given area is in general the same, although "the local sign"—that is, the point at which the animal scratches—will vary according to the point stimulated. If we take point *A* in the scratch reflex area and apply to it a stimulus which is just inadequate to produce any reflex at all, and then, while this stimulus is still in progress, apply a similar subliminal stimulus to point *B* a little removed from it, the two subliminal stimuli will become effective and produce a typical scratching movement.

In other words, the subliminal stimulus of point *A* is added at the final common path to the subliminal stimulus of point *B;* the one has reinforced the other.

In a similar way two stimuli, each of which is adequate to excite a weak reflex response from a common motor mechanism, will reinforce one another and produce a stronger response if they are applied at the same time.

The receptors from which these mutually reinforcing impulses are received need not, as in the above example, be of the same kind, similar results being obtained by stimulation of receptors of widely different kinds, such as exteroceptors and proprioceptors. For example, if a stimulus inadequate to elicit a flexion reflex is applied to the skin of the leg, and another stimulus, itself also inadequate, is applied to the central end of some deep afferent nerve in the same leg, then the two subliminal stimuli will become effective in producing a flexion movement. Allied reflexes may reinforce one another even though the exciting stimuli are applied far apart. The flexion of the fore limb which results from stimulation of the fore paw is reinforced, for example, by a simultaneous excitation of the contralateral hind foot—a stimulation that gives rise to a reflex figure involving flexion of the fore limb as we have seen in Chapter XI. Reflexes which give rise to inhibition may also reinforce one another in their action on the final common path.

Successive Combination.—The reinforcement which one reflex lends to a second allied reflex lasts for a short time after the stimulus for the first response has been removed. Consequently successive allied reflexes may reinforce one another. This reinforcement also can be illustrated in the case of the scratch reflex. If a stimulus, inadequate to excite when acting alone, is applied to a point *A* on the skin, and immediately after a second stimulus, also inadequate to excite, is applied to a point *B*, the combined effect of the two successive subliminal stimuli may give rise to a reflex response. The threshold of some common part of the reflex arc has been lowered by the effect of the preceding inadequate stimulus, even though it was applied to a somewhat remote part of the skin. For this reason a moving stimulus applied to the scratch area is far more effective than a stationary stimulus applied over the same extent of area. This phenomenon is called *immediate induction,* and it is by no means confined to the spinal cord. It is well illustrated, for example, in the case of vision. If a thin line drawn on a white card be looked at so that it falls on the edge of the receptive field of the retina, it will not be seen so well as a dot of similar width which is moved through the same distance as the line.

The Integration of Antagonistic Reflexes

Simultaneous Combination.—Two antagonistic reflexes, which use the final common path to cross purposes, naturally cannot both succeed in occupying it at the same time. We must examine what results when two such reflexes come into competition for the control of a common motor mechanism. The crossed extension reflex and the flexion reflex are two responses utilizing a common group of muscles in opposite ways. If we apply a stimulus to the skin of the leg of a decerebrate animal while the limb is extended as the result of a stimulus applied to the contralateral leg, the extension gives way completely to the flexion reflex (Fig. 49). By properly choosing the relative strengths of the stimuli a preexisting flexion reflex may also be interrupted by a crossed ex-

tension reflex. In a similar way the scratch reflex gives way before a flexion reflex. The significant fact is that *when antagonistic reflexes are in simultaneous competition for the final common path, one of them occupies the path to the exclusion of all others.* Accordingly there is no tendency for a fusion of their effects, and this is most fortunate, for fusion would only result in confusion, since the response would be appropriate for neither of the simultaneous stimuli. This is perhaps the most important principle in the integration of spinal reflexes by the final common path.

In the competition of antagonistic reflexes for the control of the final common path several principles determine the outcome. These depend on (1) the nature of the reflexes, (2) the relative intensity of the stimulus, and (3) fatigue.

The nature of the reflex is dependent on the quality of the stimulus and the purpose to which it is employed. The most prepotent reflexes are the flexions which result from the application of harmful stimuli. Their purpose is to protect the body from immediate danger and consequently they tend to displace other kinds of reflexes from occupancy of the final common path. The reflex responses to all stimuli which are capable in the conscious animal of giving rise to strongly affective sensations tend to prevail over all others, and consequently the sexual reflexes share with the responses to painful stimuli a position of dominance in the competition of reflex activity. At the opposite extreme are the postural reflexes which arise from proprioceptive stimuli and concern chiefly the extensor muscles which must support the weight of the body. These give way with facility in the face of competing reflexes of other types. It is important that they should do so, since postural tone must always adapt itself to the position into which the body has been forced in response to the stimuli of the environment.

In the case of antagonistic reflexes of equal potency the result of competition for the common path depends on the relative strength of the exciting stimuli. Thus a flexion reflex of the hind leg will usually displace a simultaneous scratch reflex, but if the stimulus eliciting the scratch is strong, and that tending to produce flexion is weak, the scratch reflex may persist and the flexion fail to assert itself.

When a reflex has occupied the final common path for some time it will become fatigued, and may then be displaced by an antagonistic reflex which could not previously compete against it successfully. Thus, ordinarily the scratch reflex is much less readily elicited than the flexion reflex, and if both are excited at the same time the latter will prevail; but if the flexion reflex is kept up until it shows signs of fatigue, then by simultaneous excitation of both reflexes the scratch reflex will obtain the mastery. The development of successive induction, which is described below, also assists the competing reflex in gaining control as its antagonist becomes fatigued.

Successive Combination.—If antagonistic reflexes occupy a final common path in succession, it is found that the use of it by one reflex facilitates its subsequent use in a movement antagonistic to that which first occupied the motor mechanism. This phenomenon is known as *successive induction.*

In the spinal animal successive induction is demonstrated by using two reflexes that are of a more or less antagonistic character—for example, the flexor

reflex and the knee jerk, or better still, the crossed extension reflex and the flexion reflex. If we elicit the knee jerk in a spinal dog at regular intervals, with stimuli of equal intensity, the extension movements (the kicks) will be approximately equal. If now we apply a nocuous stimulus to the skin of the foot and so throw the leg into flexion, it will be found, after the flexion movement has disappeared, that the knee jerk is much more pronounced than previously. Similarly, if we elicit the crossed extension reflex by nocuous stimuli of equal intensity applied to the opposite limb, the extension movements will be approximately equal. By now throwing the limb exhibiting them into the flexion reflex, the extensor movements will, of course, disappear, but after the flexion has been discontinued, they will reappear with increased intensity.

These facts show us, then, that after the final common path has been occupied by a reflex of one type, it becomes more available to a reflex of an opposite type. Successive induction gives rise to a series of responses which afford a further example of the compensatory movements produced by the integrative action of the spinal cord. By facilitating the occupancy of the final common path by reflexes opposite in nature to those which have just occupied it, movements are brought about which restore the position which was disturbed by the primary response. In other words, it is evident that if the two opposite reflexes are constantly competing with each other for possession of the final common path, they will tend alternately to occupy it, thus bringing about a rhythmic movement. Such is the mechanism involved in walking; the leg is lifted from the ground (flexion reflex); it is then brought to the ground, and the mechanical push given to the plantar surface of the foot brings out the extensor thrust, the appearance of which is greatly facilitated by the fact that, immediately before, the flexion reflex occupied the final common path.

CHAPTER XIV

POSTURAL COORDINATION AND ITS CENTRAL CONTROL

The maintenance of any posture or attitude is accomplished by the steady contraction of a large group of skeletal muscles. Such contraction differs in no fundamental manner from the muscular responses which bring about body and limb movements. An illustration of this important fact has been given in Chapter X, where it was recorded how the "postural" contraction of an extensor muscle in a decerebrate cat passes into a phasic contraction on elicitation of the crossed extensor reflex. It is usual to describe the activity of a skeletal muscle engaged in maintaining a posture or attitude as *tonus* or *tone*.

One may perceive muscle tone in the resistance which a limb offers to passive motion. If the tendon of a muscle is pulled either directly or by manipulation of a limb around a joint, the muscle actively resists the extending force. A muscle which has been disconnected from the central nervous system by section of its nerve does not offer this same resistance; it is then said to be flaccid. Since section of the dorsal roots supplying the muscle *may* abolish the tone as effectively as cutting the ventral roots, the normal resistance to passive elongation is, in such cases, a reflex of local origin. The special feature of this reflex is that both ends of the arc terminate in the muscle itself. The sense organs are proprioceptors stimulated by stretch and situated within the muscle. As Sherrington has pointed out, the stretch reflex is tonus in the making. A consideration of the physiology of posture should therefore begin with a consideration of this fundamental reaction.

THE STRETCH OR MYOTATIC REFLEX

The intimate nature of this response was first demonstrated by Liddell and Sherrington.[169, 170] In their study they employed the extensor muscles of the hind limbs of the decerebrate cat. The exaggerated tone in these muscles makes them especially favorable objects for such a study, since, as we shall see, it is the result of an overactive stretch reflex.

In their experiments Liddell and Sherrington functionally isolated the particular muscle used (for example, the quadriceps) by paralyzing all other muscles in both hind legs by section of their nerves or tendons, and the skin was also excluded as a source of extraneous stimuli by denervation or suitable protection. Therefore any sensory stimulation or reflex effect produced by stretching such an isolated muscle must be solely due to the stretch itself. The tendon of the muscle to be studied was attached to an isometric myograph, and the femur was fastened rigidly to the table on which the trunk lay. The top of this table was arranged so that it could be moved up and down under the myograph so as to slacken or pull on the tendon at a rate and to an extent corresponding to the natural movements of the knee joint. The nature of the record obtained on lowering the table top is shown in Fig. 53.

The amount of tension developed by a muscle as a result of stretch is, of course, partly due to mere dead stretch of tissue. To this passive tension is added tension which is the result of active contraction, as can be demonstrated by denervation. In Fig. 53 the reflexly developed tension is shown by the difference between curves *P* and *M*. Further proof of the reflex origin of this active re-

sponse to stretch is given by the fact that it may be reflexly inhibited, for example, by elicitation of the ipsilateral flexor reflex. On the principle of reciprocal innervation of antagonistic muscles the discharge to the extensors is then inhibited, and their reflex contraction is abolished (Fig. 53). The stretch response is divisible into two parts: a phasic contraction consisting in development of tension during the increment in stretch, and a static or postural contraction during the maintenance of a steady stretch. The phasic stage is the counterpart of a tendon jerk, for when a tendon of a muscle is tapped where it is not supported by underlying bone, its muscle undergoes a sudden brief stretch. Tension receptors thus stimulated send to the cord an almost synchronous volley of afferent impulses which, passing over the central paths of the reflex arc, produce sufficient summation to excite a motor discharge. By virtue of the slow adaptation of the stretch receptors (Chapter IX), a long-continued stretch produces a continued reflex excitation; that after-discharge is not the cause of this follows from the fact that the reflex tension drops immediately upon removal of the stretch.

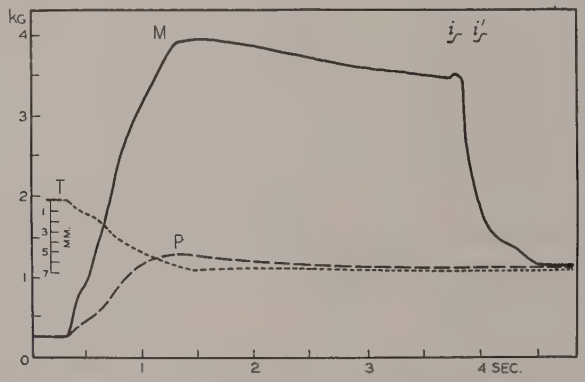

Fig. 53.—The stretch reflex of the whole quadriceps (cat). Muscular response *M* before, and *P* after cutting nerve to the muscle. *T* is a record of the table-fall which stretches the muscle. At right is shown the effect of reflex inhibition, evoked between *i* and *i'* by stimulation of afferent fibers in ipsilateral peroneopopliteal nerve. (From Liddell and Sherrington: Proc. Roy. Soc. **96, B:** 212, 1924.)

Distribution of the Reflex; Slow and Rapid Muscles.—Stretch reflexes are especially well developed in those muscles whose contraction habitually furnishes the pull necessary to maintain a posture or an attitude against the force of gravity. Thus they are found in the extensors of all the joints of the extremities and in the closing muscles of the jaw. Now it has been shown (Denny-Brown[160]) that in the musculature of mammals fibers of similar speed of contraction are arranged together in groups which are sharply delimited from other groups. Usually these groups form different "heads," or they may be separated simply by a layer of fascia as in the case of supraspinatus, which in the cat is an extensor of the shoulder. As a rule the extensor complex acting at any one joint possesses two components which differ in respect to speed of contraction, for example, at the ankle, gastrocnemius (rapid) and soleus (slow). The twitch of soleus is on the average three times as long as that of the corresponding gastrocnemius, and similar differences are found between the slow and rapid com-

ponents of other extensor groups of muscles. Flexor muscles are almost invariably rapid. Figures for the contraction times of several muscles have been given on page 16. Fig. 54 illustrates the typical difference between the twitch duration of a rapid (semimembranosus) and a slow muscle (soleus). Because of their long twitch durations slow muscles are tetanized at a lower frequency of stimulation and are therefore more economical in maintaining tension. They appear to be especially adapted for the execution of postural contractions reflexly evoked by a low frequency discharge of impulses from the central nervous system.

A difference in the color or shade of different muscles is a common observation. Even among mammals there are light and dark striated muscles; in the rabbit pale and red muscles are obvious and a similar difference of less degree can be made out in the muscles of the cat. It has often been suggested that all red muscles are slow and all white muscles are rapid, but Denny-Brown[160] in a study of the relationship between the speed of contraction of mammalian muscles and their histological features concluded that although redness (red pigmentation) is closely associated with slowness of contraction this is only a chance association. There are many exceptions. Denny-Brown points out, for example, that "redness of muscle in the adult cat is a fairly reliable guide to slowness of contraction, but a

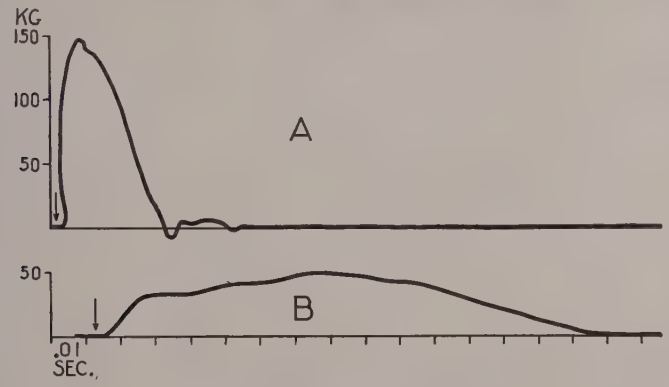

Fig. 54.—The twitch contraction of a rapid (pale) muscle compared with that of a slow (red) muscle. Rabbit's semimembranosus (*A*) and soleus (*B*). Note the conspicuous difference in the durations of the two simple contractions. The time for both curves is shown in 0.01 sec. intervals below *B*. (Record by Hay, from Fulton: *Physiology of the Nervous System*, New York, 1938, Oxford University Press.)

crureus is often as red as the soleus, and yet shows only a quarter of the twitch duration of that soleus." There is no evidence that redness has any relation to a special respiratory mechanism which permits the muscle to withstand fatigue. Many histological features of muscle have been regarded as indices of slowness or rapidity of contraction, but Denny-Brown's studies have led him to the conclusion that there is no histological criterion of the speed of contraction of a muscle fiber.

It has been clearly demonstrated by Denny-Brown[159] that stretch reflexes are much more prominent in the slower extensor muscles than in any other components of the body musculature. He found not only that they have a lower reflex threshold for stretch but also that the proportion of fibers which can be reflexly stimulated to contraction by extreme degrees of stretch is very much less in rapid than in slow extensor muscles. The physiological flexor muscles belong to the rapid group and they do not, as a rule, show any sustained reflex contraction in response to stretch, although the occurrence of flexor tendon jerks

and "pluck reflexes" shows that the phasic part of the reflex may be elicited in some of them. Liddell and Sherrington found that stretching a knee flexor reflexly inhibits the stretch reflex of its antagonistic extensor muscle. This kind of response, which is probably widespread, is of obvious importance in relation to the mechanism of stepping.

Grading of Response.—The amount of response and its rate of development are proportional to the amount and rate of stretching. Furthermore, the response to local stretching is, in most extensor muscles, strictly local, only that part of the muscle responding which is actually stretched. In this way the reflex affords an excellent basis for a postural contraction nicely adapted to the weight which must be supported. The reflex discharge to a stretched extensor muscle is at a low rate (7-20 impulses per second) over each motor fiber, and discharges in the active fibers are markedly asynchronous.[159] It has been emphasized in a previous chapter that the subtetanic contractions produced by this sort of discharge are singularly insusceptible to fatigue. Denny-Brown[159] has shown that in the course of a sustained stretch reflex individual fibers maintain their activity continuously; they do not drop out of the response to be replaced by other fibers previously silent. In other words, no sign of rotation of activity was ever observed among the elements of a muscle engaged in this postural reaction. Grading of the stretch reflex is achieved by change in the number of motor neurons firing, rather than by increased frequency of discharge over already active fibers, thus preserving the advantageous subtetanic peripheral activity.

Lengthening and Shortening Reactions.—The stretch reflex which we have been considering is a response to reflex excitation which has its origin in the very muscle which responds. This is an instance of *autogenous excitation.* A muscle may also be influenced reflexly by *autogenous inhibition.* If the hyperextended limb of a decerebrate preparation be passively flexed at the knee, strong resistance is felt, but on continuing to bend the joint this suddenly gives way and a "clasp-knife" effect is obtained. This is the *lengthening reaction;* it signals the partial or complete abolition of the stretch reflex. The explanation is that the muscle contains a species of end organs sensitive only to excessive stretch and that these discharge afferent impulses which inhibit the myotatic reflex. Their function is obviously one of protection. Their stimulation, like that of cutaneous pain receptors, leads not only to ipsilateral flexion, but also to extension of the opposite leg (Philippson's reflex). After yielding a lengthening reaction, a limb can be passively extended without encountering resistance, but if forcible flexion is attempted from this new position, strong resistance is again felt. This is the *shortening reaction.* "It seems probable that here the relief of tension during the execution of the 'shortening' lessens the autogenous reflex excitation for the time being, but this sets in again on cessation of that relief."[117] The peculiar "plastic" quality of decerebrate rigidity and allied states of hypertonia is due to these two reactions.

The Stretch Reflex as a Spinal Mechanism.—Fundamentally the stretch reflex is a spinal process. It may be elicited in a hind limb extensor muscle after the lumbar region of the cord has been isolated by low spinal transection, but only after recovery from spinal shock. The phasic part, however, is less subject to spinal shock than the static or postural component. A brisk knee jerk may be evoked early in the spinal state at a time when the postural part of the myotatic reflex is absent or feeble, tension falling off rapidly with continued

stretch. After recovery from spinal shock the static component returns in certain extensor muscles where, in fact, it may become evocable in the form characteristic of the decerebrate state.[161] Nevertheless, stretch reflexes in spinal preparations do not have the wide distribution found in decerebrate animals, nor are spinal animals ever capable of the degree of "reflex standing" shown by the decerebrate. It is clear that descending impulses of supraspinal origin reinforce the stretch reflex. We must turn to an examination of this fact in order to gain further insight into the management of posture by the central nervous system.

DECEREBRATE RIGIDITY

In most mammals there ensues upon mesencephalic transection of the brain stem a condition characterized by a peculiar *distribution* of tone in the body musculature. Those muscles whose action normally opposes the force of gravity exhibit a high degree of resistance to passive elongation, while their antagonists are relatively flaccid. In the complete absence of external stimulation and regardless of the position in which it is placed, the decerebrate cat, dog, or monkey remains with limbs rigidly extended, head and tail dorsiflexed, jaw tightly closed, and back straight. If put in a standing position, it will stand, but only so long as it is balanced (Fig. 41). The body, head, and tail do not yield to the force of gravity, the back does not become convex, and the lower jaw is held tightly against the upper.

The most reasonable interpretation that can be given this remarkable postural state is that it represents the activity of a central antigravity mechanism, released from the control of higher centers and accentuated by the absence of modifying postural reactions and locomotion. The antigravity nature of the activity is emphasized by the fact that the sloth, an arboreal edentate, which habitually hangs upside down, shows, on decerebration, a marked preponderance of tone in the flexor muscles; the legs, head, and tail are held rigidly flexed (Richter and Bartemeier[176]).

The contraction of the antigravity muscles in decerebrate rigidity is reflex in origin, for it can be abolished by section of appropriate nerves or elimination of certain reflex stimuli. In the case of the hind legs, the extensor hypertonia may be reduced by section of the dorsal roots which carry the afferent fibers from the extensor muscles themselves. It may also be abolished by eliminating any pull on them. Section of nerves from other muscles in the leg or from the skin affects the rigidity not at all.[149] These facts show that the stretch reflex of the extensors is an important factor in the production of their rigidity. It is not, however, the only factor, for it has been found that some time after deafferentation the hind legs of a cat develop typical extensor hypertonia when the animal is decerebrated.[174] Under such circumstances the rigidity has its reflex origin in the labyrinthine proprioceptors and in the stretch receptors of the neck muscles. (See tonic neck and labyrinthine reflexes, page 137.) The rigidity of the forelegs is not reduced by deafferentation, and it is clear that proprioceptors of neck and ear constitute its essential source.[174] Since stretching a "slow" extensor muscle only slightly invariably augments the rigidity, the condition is one in which the stretch reflex has a low threshold. This is apparently by virtue of the large amount of summation of afferent impulses from several groups of receptors. We shall see that it is also due to an absence of the normal amount of inhibition.

The Central Nervous Mechanisms Involved in the Production of Decerebrate Rigidity.—In his original description of this condition Sherrington stated that it followed transection of the brain stem through the caudal part of the diencephalon or at any mesencephalic level. It is common practice to produce it by severing the brain stem just between the anterior and posterior corpora quadrigemina (Fig. 41). The typical rigidity then appears on removal of the anesthetic. It survives successive transections until these reach the level of entry of the eighth pair of cranial nerves. Cutting through the bulb in this region or at any level below it produces the postural condition characteristic of the spinal state. Evidence has accumulated to show that in the carnivore decerebrate rigidity depends on the integrity of one or more of the vestibular nuclei, more especially Deiter's nuclei, and that it is due to impulses descending by way of the uncrossed vestibulospinal tracts. If a localized lesion is made in the region of Deiter's nucleus so that degeneration of the vestibulospinal tract occurs, subsequent mesencephalic transection fails to produce rigidity on the side of the injury and degeneration, although hyperextension appears in typical form in the legs of the intact side (Fulton, Liddell and Rioch[165]).

The activity of the vestibulospinal system in producing the rigidity might be the result of "irritation" set up by the operative insult. This possibility is rendered unlikely by the fact that electrical stimulation of the cut surface of the brain may abolish or reduce the rigidity; it does not intensify it. Bazett and Penfield[156] were able to keep alive a number of decerebrate cats for periods of time (from two to three weeks) sufficient to assure degeneration of all descending fibers cut by the low mesencephalic transection. The rigidity persisted. Such results demonstrate that decerebrate rigidity, dependent on activity in the vestibulospinal system, is a release phenomenon resulting from the removal of some inhibitory influence of suprabulbar origin. The latter certainly emanates from several parts of the brain. The view, which was put forward by Magnus[172] and Rademaker and widely accepted, that decerebrate rigidity is chiefly the result of destruction of the red nuclei can no longer be entertained. Ranson[167] and his collaborators have shown that after complete destruction of the red nuclei by narrowly restricted mesencephalic lesions, cats fail to show the typical rigidity. Such animals are capable of righting themselves, standing in normal fashion, and walking, and when suspended with feet off the ground show a very mild extensor hypertonia not at all comparable to that seen in the decerebrate preparation. In cats and dogs the greater portion of the inhibitory influence has its origin above the mesencephalon.[166] Although chronically decorticate animals exhibit a fairly normal distribution of tone when standing, sitting, or walking (Fig. 43), their legs become rigidly extended and strongly resist passive flexion when the animal is held suspended in the air.[155, 269] This condition is quite comparable to the rigidity of the decerebrate preparation; it demonstrates that the removal of a cortical influence is the most important factor in the development of decerebrate rigidity (see discussion by Bard and Rioch[269]). A mesencephalic influence is doubtless of some importance in the maintenance of a normal distribution of tone, and a similar restraint originates in the cerebellum (see page 169). The corticofugal impulses which inhibit extensor tone descend from the region of the electrically excitable motor cortex,[179] but according to Tower[178] they are not mediated by the pyramidal tract.

The experimental facts concerning decerebrate rigidity lead to the important conclusion that the normal distribution of tone among the antigravity muscles is the resultant of a number of influences, both excitatory and inhibitory, which act upon the final common path. Impulses over the vestibulospinal tracts and over afferent fibers from certain proprioceptors augment the motor discharge. From certain proprioceptors, from the cerebral cortex, the cerebellum, and other parts of the brain, impulses originate which directly or indirectly inhibit the motor discharge. The analysis of this abnormal condition has unquestionably thrown much light on the nervous management of posture in general. Further, it is an excellent demonstration of how the central nervous system is organized on the basis of a series of checks and balances.

Decerebrate rigidity follows low mesencephalic transection in all the higher mammals. True decerebrate rigidity has been seen in man, but many of the patients described as exhibiting this phenomenon have really been cases of decorticate rigidity. We have seen that the distribution of tone which follows decortication in cats and dogs bears a strong resemblance to decerebrate rigidity, but in all primates decortication or bilateral removal of the precentral motor areas of both cortices is followed by a distribution of tone which especially in the arms is quite different from that which is seen when the lower brain stem is transected (see Fulton[124]). In both conditions the legs are strongly extended, but after the cortical removal the arms are held semiflexed in the typical hemiplegic posture (see Chapter XIX), whereas true decerebration imposes on the upper extremities a posture of rigid extension. Cases of decerebrate rigidity in man are rare; the syndrome is usually produced by a hemorrhage or a tumor invasion which functionally transects the mesencephalon.

ATTITUDINAL AND POSTURAL REACTIONS

Attitudinal Reflexes.—We have seen that the hyperextension of the extremities of a decerebrate animal may be modified by elicitation, through nociceptive stimulation, of one or another reflex figure (Chapter XI). Magnus and de Kleijn[171, 172] showed that a similarly harmonious relation of the different parts of the body may be produced by passively changing the position of the head. If the head is forcibly ventroflexed, the postural contraction of the extensor muscles of the forelegs is inhibited, and the fore quarters sink, while at the same time the postural contraction of the extensors of the hind legs increases, raising the hind quarters. The animal assumes the proper attitude for looking under a shelf. On the other hand, if the head is passively dorsiflexed, the forelegs extend further and the hind legs flex. The attitude is now that of a cat looking up at a shelf and ready to spring. If the head is turned to one side, say the right, the displacement of the center of gravity is compensated for by the increased extension of the right legs, while the left are flexed, ready, as it were, to take the initial step. These are the *tonic neck reflexes.* They originate in neck proprioceptors, and they last as long as the head retains the new position. *Tonic labyrinthine reflexes,* elicited by change of the position of the head in space, affect all four legs similarly. The influence of the labyrinth in the decerebrate preparation can be studied separately after excluding the neck reflexes by section of the upper cervical dorsal roots or by fixating the head and body in a plaster cast. Extensor tonus of labyrinthine origin is maximal when the animal is supine with the angle of the mouth 45° above the horizontal; it is minimal when the animal is prone with the angle of the mouth 45° below the horizontal. When the head is brought into other positions by rotation of the body around its transverse or longitudinal axis, intermediate degrees of extensor tonus result. The tonic neck and labyrinthine reflexes sum algebraically when

both are elicitable. These reactions may be observed in normal animals in which they are evoked by active as well as passive movements of the head. They are easily evoked in monkeys after removal of the frontal lobes[124] and in children with severe damage of the higher motor mechanisms of the brain.[158]

These postural reactions are brought about by motor discharges of slow rate and they operate through the same spinal mechanism which manages the stretch or myotatic reflexes. It was shown by Denny-Brown[159] that the tonic neck and labyrinthine reflexes influence the stretch reflex just as they influence the posture of the limb. They involve the slow extensor muscles far more than the rapid ones (Fig. 55) and when the response is small, it is seen only in the former group. It is plain that the stretch reflexes, which as we have seen are essentially spinal in origin, can be modified by impulses originating in the labyrinth or in proprioceptors of the neck muscles. When in a decerebrate animal the afferents from all limb muscles are interrupted by section of the appropriate dorsal roots, these and other sources of excitation may maintain slow rates of motor discharge to the postural muscles. It is for this reason that extensor rigidity appears in deafferented limbs after decerebration.

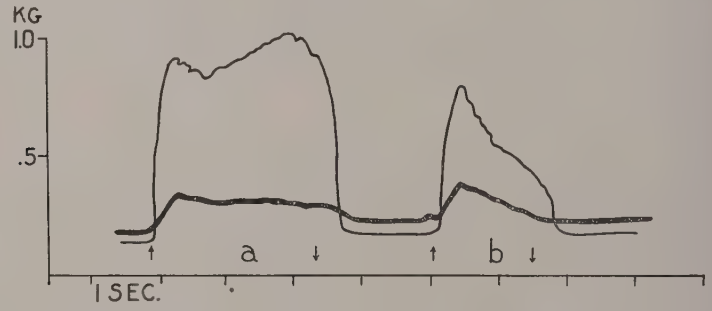

Fig. 55.—The effects of tonic neck reflexes on slow (red) and rapid (pale) muscles in the decerebrate preparation. Thick line is record of reflex contraction of the short lateral head (fast) of the triceps; thin line, reflex contraction of the short medial head (slow) of triceps. Neck dorsiflexed at ↑ and ventriflexed at ↓. Labyrinth in intermediate position in each neck posture. (After Denny-Brown[118] from Fulton: *Physiology of the Nervous System*, New York, 1938, Oxford University Press.)

Normal Standing.[175]—Decerebrate rigidity has been described as "reflex standing." The standing of the decerebrate preparation is, however, a mere caricature of normal standing. Comparison shows that the two conditions differ in several important respects as regards this fundamental postural achievement.[175] An enumeration of these differences will reveal something of the character of normal standing and the extent to which suprabulbar mechanisms contribute to normal postural activity.

1. The distribution of tone in the musculature is quite different in the two cases. In the decerebrate animal the postural contraction of the extensors is accompanied by diminution of the tone of the flexors, whereas in normal standing all the muscles around the joints of the limb are strongly contracted so as to fix the limb in the form of a rigid pillar.

2. If the decerebrate animal is placed on its side or back, it remains in that position, never showing the slightest tendency to right itself. Normal animals succeed in maintaining themselves right side up under the greatest variety of disturbing conditions.

3. The decerebrate animal keeps its legs rigidly extended regardless of its position. It never places its feet in the correct position for standing. In contrast, the normal animal actively places its feet in such a way that a normal stance can be assumed.

4. If a decerebrate animal is placed in a standing position, the slightest shifting of its body to one side causes it to topple over. The normal animal, however, by executing correcting movements of the legs, succeeds in maintaining the standing posture during horizontal displacement of the body.

5. When made to stand on an inclined surface the normal animal adjusts the distribution of tone in its muscles in such a way as to buttress itself against the effect of the consequent shift in its center of gravity. No trace of such a response is seen in a decerebrate preparation subjected to these conditions.

These deficiencies of decerebrate standing are the result of the absence of certain specific postural reflexes. We shall next consider the more important of these reactions.

The Supporting Reactions.—Limbs which are freely movable when they are used in stepping or as instruments for prehension, scratching, fighting, and so forth, are transformed during standing into rigid pillars which give the impression of being solid columns for the support of the body. Experiments by Magnus[172] and his collaborators (Schoen, Pritchard, and Rademaker) have shown that this is accomplished by a series of local static reflexes. The development of the pillarlike state is called the *positive supporting reaction.* It is in part brought about by an extensor response to the exteroceptive stimulus evoked by the contact of the feet with the ground (*magnet reaction*). It is more especially the result of the proprioceptive stimuli set up in the flexor muscles of the distal joints (digits, wrist, ankle) when these are stretched by the pressure of the foot on the ground. A complex stretch reflex is thereby set up which involves not only the stretched muscles themselves but also the co-contraction of extensors and flexors, abductors and adductors, around each joint, so as to fix the entire limb for standing. In addition the muscles of the back take part and their participation is especially well seen when the whole reaction has been exaggregated by decerebellation (Fig. 62). The resolution of this response is not wholly due to cessation of the stimulus, for active processes set up by stretching the extensors of the distal joints take part in loosening the limb. This is the *negative supporting reaction.* In the decerebrate animal these reactions are not present; instead there is only the overactive stretch reflex of the extensors. After removal of the cerebral cortex the supporting reactions are disturbed profoundly, but are not entirely absent (Rademaker).

The Righting Reactions.—The ability to stay right side up is a universal property of animal organisms. Magnus and de Kleijn have shown how, in the higher animals including ourselves, this capacity is dependent on a group of specific righting reflexes.[171, 172] These responses can best be studied in decorticate animals in which their reflex nature is quite apparent. If such an animal is held up by the pelvis, the head is kept in its normal position as the body is turned from one side to the other or allowed to hang down. The compensatory movements of the head are *labyrinthine righting reactions* which are set up by stimulation of the otolithic apparatus. The responding muscles are those of the neck. These righting movements fail to occur in animals without labyrinths, and they are abolished by removing the otoliths from their maculae. So long as a

decorticate or blinded animal without labyrinths is held in the air, its head takes a passive position imposed by gravity, but the moment it is placed on its side on the ground, the head is righted into the normal position. The response is due to asymmetric stimulation of the body surface, as can be shown by the fact that placing a weighted board on the uppermost side causes the head to go back into the lateral position. This is a *body righting reflex acting on the head.* When the head has been righted by either of the reflexes acting upon it, the resultant twisting of the neck excites, proprioceptively, a *neck righting reflex* which first causes the thorax, then the lumbar region, and finally the pelvis to follow the head into the normal upright position. *Body righting reflexes acting on the body,* elicited by asymmetric stimulation of the body, may, however, cause the body to right itself even when the head is held in the lateral position. Finally, in the higher mammals (cats, dogs, and monkeys) righting reflexes may be initiated through visual stimuli. The *optical righting reflexes* result in the orientation of the head and are capable of bringing this about in the absence of labyrinthine or body stimulation. They are dependent on the cerebral cortex. The centers for the nonvisual righting reflexes lie chiefly in the medulla and mesencephalon, but chronically decorticate cats show a very marked deficiency of the labyrinthine righting reaction.

The Placing Reactions.—A primary requirement for normal standing is that the feet should be placed in the proper position. The normal animal accomplishes this through the agency of a group of placing reactions which have been described by Rademaker[175] and by Bard.[154, 268] When the animal is lowered toward a supporting surface visual stimuli cause the forelegs to be put down in such a way that without further adjustment they support the body in standing. With vision excluded, various exteroceptive and proprioceptive stimuli, resulting from contact, position, or movement, elicit other placing reactions which serve the same purpose, namely to bring the legs from any nonsupporting pose into a standing position.

Five nonvisual placing reactions may be distinguished. A brief description of them will serve to show how rich is the equipment for the attainment of this one postural result.

1. If a cat is held in the air with the legs free and dependent and with the head held up (so that it cannot see its forefeet or any object below and in front), the slightest contact of the backs of either pair of feet with the edge of a table results in an immediate and accurate placing of the feet, soles down, on the table close to its edge (Fig. 56).

2. If the forelegs of a cat suspended in the air are held down, and the chin is brought in contact with the edge of a table, both forefeet on being released are instantly raised and placed beside the jaws. Usually this is followed by extension, so that a standing position is quickly assumed. If a blinded animal is used, the forefeet, even though not held down, remain hanging until the chin touches the table.

3. If the forelegs or hindlegs of a cat that is standing, sitting, or crouching on a table, are thrust over the edge, they are immediately lifted so that the feet quickly regain their original positions on the table.

4. If any leg of a standing cat is passively abducted without being held, it is at once adducted and lowered so as to restore the foot to its normal standing position.

5. Although each of the foregoing reactions may be adequately studied in animals with vision intact, this final one can be evoked in pure form only after blindfolding, enucleation of the eyes, or removal of the visual cortex. The animal held in the air with the forelegs free is moved toward some solid object. As soon as the tips of the vibrissae of one or both sides touch the object, both forefeet are accurately placed on it. Unless the influence of the eyes is excluded, a visual placing reaction of the forelegs will be evoked under these circumstances.

Hopping Reactions.—These are essentially corrective movements of the legs which serve to maintain a standing posture under conditions involving displacement of the body in the horizontal plane. They are demonstrated by holding the animal so that it stands on one leg. Then on movement of the body forward, backward, or to either side, the leg hops in the direction of the displacement so that the foot is kept directly under shoulder or hip (Fig. 63). Rademaker[175] showed that a disappearance of the supporting tone of the leg is an

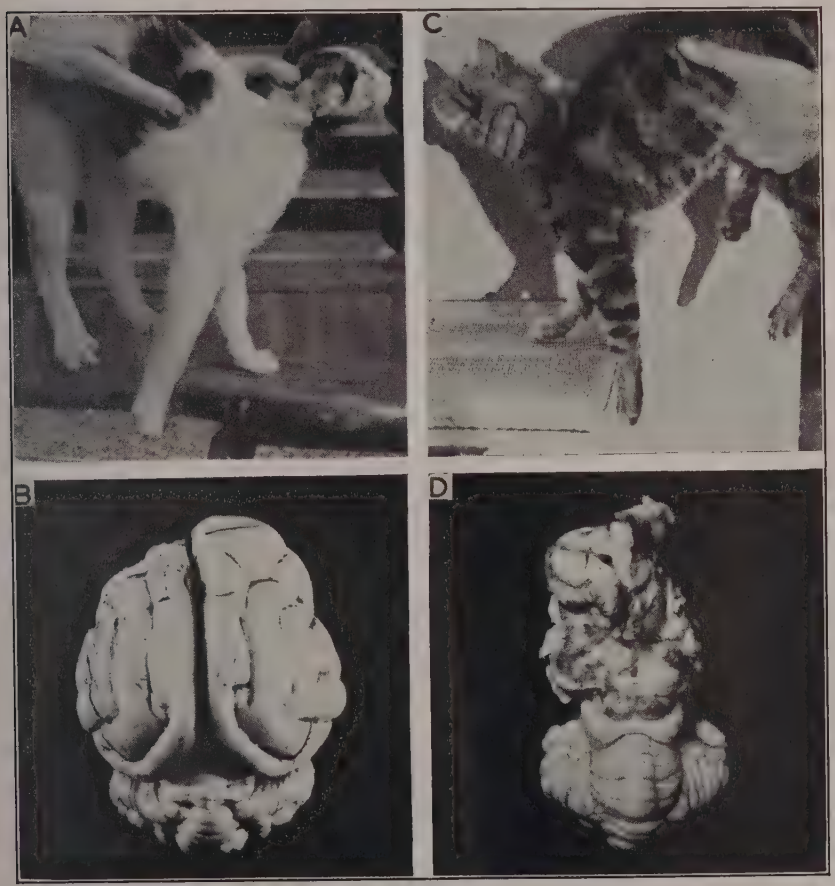

Fig. 56.—Photographs which indicate the nature and the localized cortical control of the placing reactions of the cat. *A* is a picture of an animal whose brain is shown below in *B*. Removal of a small area of cortex at the frontal pole of the left hemisphere has permanently abolished the placing reaction of the right foreleg which occurs when the dorsum of the foot is lightly touched to the edge of a supporting surface (top of stool). As can be seen in *A*, the ablation has not affected the response of the ipsilateral foreleg. The defect is as great as that shown by animals from which the entire cortex of one side has been removed. *C* shows a cat which had been subjected to removal (in two stages) of all cortex except the frontal area which was ablated in the other animal. Its brain is shown in *D*. Note that the cat has placed the right foot. This and other tests show that the small remnant of the left cortex was capable of managing in normal fashion the nonvisual placing reactions and the hopping reactions of the opposite (right) foreleg. (Adapted from Bard: Arch. Neurol. and Psychiat. **30:** 40, 1933.)

integral part of each hopping reaction. With the leg in the median standing position the positive supporting reaction is strong, and the leg is acting effectively as a rigid pillar, but with any displacement of the body that induces a deviation from the median position, the supporting tone diminishes, the foot is raised, transposed in the direction of the displacement, and put down again to give a median support for the body in its new position. It is probable that these reactions are caused by the stretching of one or another group of muscles, i.e., that they are myotatic in origin.

The Central Control of the Placing and Hopping Reactions, an Example of Strict Localization of Function.[154, 268]—When in a cat the entire cortex of one cerebral hemisphere is removed the nonvisual placing reactions of the contralateral legs completely disappear and do not return during long survival periods (six months to six years).* The hopping reactions are permanently depressed; some cannot be elicited while others are retarded, weak, and so slow that the movement is not repeated rapidly enough to keep pace with even slow displacements of the body. Unilateral decortication does not affect the reactions of the legs ipsilateral to the removal. The control is entirely contralateral. After bilateral decortication the loss and deficits are bilaterally equal. An ablation of the frontal pole of one cortex of the extent shown in Fig. 56, *B* produces as great a deficit of the reactions of the opposite legs as does complete unilateral decortication. The cortical area necessary for the elicitation of these responses includes most of the cortical points, stimulation of which causes movements of the contralateral legs. Removal of any other cortical area has no effect on the reactions. Indeed, one may remove all cortex except the frontal pole of one hemisphere (Fig. 56, *D*) without disturbing the reactions in the legs contralateral to the remnant. The fact that a remnant of rostrally situated cortex is able to manage in normal fashion the placing and hopping reactions shows conclusively that the cortical control of these responses is strictly localized and functionally independent of all other cortical areas.

This is an instance of the strictest kind of localization of function in the cerebral cortex. In general it may be said that the term "localization of function" has been used in a rather loose sense. Since evidence indicates that different functions have quite different degrees of dependence on specific cortical areas (page 236), localization may be regarded as a relative matter. To apply a rigorous definition, however, it may be said that a cortical function is localized only when a small area contains all the tissue essentially concerned in the cortical control of that function. To demonstrate such localization, it is not enough to show that the function is regularly and permanently abolished by extirpation of a restricted area, for remaining areas may act through it. To conclude that a cortical function has its sole residence in a restricted area it is necessary to show that the function is not affected by removal of all cortex except this area. As can be seen, this has been accomplished in the case of cortical management of the placing and hopping reactions.

It is in accord with our general conception of cortical functions that these cortically managed reactions have to do with the finer adjustments of postures which are developed by subcortical levels of integration.

From the point of view of comparative neurophysiology it is of interest that in the monkey all hopping reactions as well as the placing reactions are completely abolished by a cortical removal (ablation of motor cortex).[268] In the reptile such of these reactions as are

*A proprioceptive correcting or placing response allied to the hopping reactions remains and may become quite prominent. It consists in a placing of the foot, clumsily and often slowly, when, in attempting to elicit reaction (1), the leg is retroflexed. This is not to be confused with the tactile placing reaction.

present depend upon central mechanisms lying below the telencephalon. In the rat and rabbit reactions quite similar to those of the cat described above occur, but they are less well developed, and on decortication they are definitely less affected. Thus in the ascending scale of vertebrate quadrupeds the central control of these particular postural responses becomes more and more "corticalized." In the monkey the control can be analyzed in terms of the cortical sensory and motor components.[268]

THE ROLE OF THE LABYRINTHS IN THE CONTROL OF POSTURE AND MOVEMENT

We have already encountered instances in which the labyrinth contributes to the production of normal posture. The nonauditory part of this complex receptor organ exerts a great many influences whose summation contributes greatly to postural efficiency. We can consider only a few of these. The interested reader is referred to the excellent account by Dusser de Barenne[163] for detailed information on this subject.

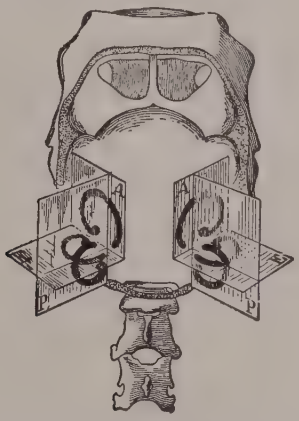

Fig. 57.—The semicircular canals of the ear, showing their arrangement in the three planes of space. (From Howell's Physiology.)

Anatomical Considerations.—The labyrinthine proprioceptors are the sense organs of the semicircular canals and of the utricle and saccule. They are to be distinguished from the receptors of the cochlea and may therefore be referred to as the nonauditory labyrinthine receptors. A sense organ, the *crista,* is found in the ampulla of each semicircular canal and a similar receptor, the *macula,* is situated in the utricle and the saccule. Each of these five organs consists essentially of elongated sensory epithelial cells and non-sensory supporting cells. The former carry long extensions called *sensory-hairs* which are embedded in a gelatinous mass covering the surface of the crista or macula. In the case of the cristae this mass (the cupula) extends across the ampulla and touches the opposite wall. The distinguishing feature of the maculae is that the gelatinous mass is covered with microscopic crystals or concretions of lime, the *otoliths.* Because of this the receptors of saccule and utricle are often called the *otolith organs.*

The sense cells of the cristae and maculae receive the peripheral terminations of the afferent neurons of the vestibular portion of the eighth nerve. These neurons, which are bipolar, have their cell bodies in the ganglion of the vestibular nerve and their centrally directed axons make connections chiefly with the cells of the primary vestibular nuclei. Some vestibular fibers proceed, however, directly to the cerebellum.

The semicircular canals, utricle, and saccule are parts of the membranous labyrinth which is filled with *endolymph.* The space between the membranous labyrinth and the walls of the bony labyrinth is occupied by the *perilymph.*

The three semicircular canals, *anterior, posterior,* and *external,* are arranged in the three planes of space (Fig. 57). The anterior and posterior canals are vertical, for they lie at an angle of about 45° with the frontal and sagittal planes of the skull. The external canal, which is usually called the horizontal, is in the human being actually inclined backwards and downwards at an angle of about 30° to the horizontal plane of the skull.

Effects of Labyrinthectomy.—It has long been known that in the lower animals destruction of the labyrinth causes very abnormal postures to be assumed and that these can largely be attributed to unusual conditions of tone in the neck muscles. In case of bilateral labyrinthectomy a great loss of tone in the muscles of the body results, at least temporarily. If the organ on one side only is destroyed, abnormal postures of the head result from the unequal influence of the remaining labyrinth on the tone of the neck muscles. The result is a continuously acting righting reflex which causes the trunk to be curved and makes the animal tend to roll over and over laterally. After some time compensation occurs, these forced movements and postures tend to become less conspicuous and the animal is chiefly remarkable for the deficiencies which it shows, deficiencies which represent the complete absence of the reactions to labyrinthine stimulation which are described below.

Comparative studies show that the severity of the disturbances created by unilateral or bilateral labyrinthectomy diminishes as one ascends the phylogenetic scale. This difference is seen even within the group of primates; for example, in the baboon the disability resulting from extirpation of the labyrinths is much less severe than in the rhesus monkeys.[162] Section of the eighth nerve or of its vestibular portion, a procedure which is equivalent to labyrinthectomy, when carried out in the human subject (Dandy; McKenzie) produces only mild and transitory disturbances, but it of course leaves the patient devoid of all reflexes of vestibular origin. It appears that in the higher mammals, especially in man, other mechanisms, chiefly those of muscle sense and vision, subserve functions which in the lower forms depend primarily on the play of afferent impulses from the labyrinthine proprioceptors.

The Two Types of Labyrinthine Reflexes.—The functions of the semicircular canals were first differentiated from those of the utricle and sacculus by Breuer in 1875. He stated that the ampullar cristae are receptors for responses due to rotations, while the maculae give rise to responses dependent upon the position of the head in space and upon rectilinear motion. From that time on it has been customary to speak of two main groups of labyrinthine reactions: (1) the *statokinetic* or *labyrinthine acceleratory reflexes* and (2) the *static* or *labyrinthine positional reflexes* (see Dusser de Barenne[163]). The first group is evoked by active or passive movements of the head and the effective stimulus for them is not the velocity of movement, but acceleration (changes in velocity), whereas the second group is evoked by the position of the labyrinths in space. The acceleratory reflexes are typically phasic, the positional tonic in the sense that they persist as long as the position does not change.

Acceleratory Reflexes.—One of the simplest of the responses to acceleration is easily demonstrated in a cat. If the animal is blindfolded, held by the pelvis with the head down and then suddenly lowered through the air, the forelegs are extended and the toes spread. This response to *linear acceleration* disappears after bilateral labyrinthectomy, but a similar reaction mediated through the eyes remains. Both are of use to the jumping animal in effecting a landing on the feet.

Upon *angular acceleration* responses are evoked in the muscles of the eyes, neck, limbs, and trunk. The reaction shown by the eyes is called *nystagmus*. This phenomenon can be observed in a man or an animal during and after rotation. As the head turns the eyes swing slowly in the opposite direction in an attempt to maintain their fixation. Having turned as far as possible they swing quickly back in the opposite direction to fix a new object which in turn they follow by a slow deviation. Nystagmus therefore consists in a slow deviation alternating with a rapid movement in the opposite direction. The direction of the nystagmus is customarily designated as that of the quick phase. During rotation the direction is the same as that of the rotation. If the rotation is continued for some time at a constant rate, the nystagmus gradually dies away, an example of the fact that this type of reaction depends upon acceleration, not on velocity. If the rotation is suddenly stopped the eye movements begin again, but now the direction of this postrotatory nystagmus is just the opposite of that which occurred when the rotation was begun; again we see that acceleration, negative in this case, is the effective stimulus. The reversal in direction takes place of course if the rotation is stopped before the initial nystagmus has ceased. Nystagmus may be horizontal, vertical, or rotatory. The type depends on the relation of the semicircular canals to the plane of rotation. For example, when the head is placed so that the horizontal canals are in the plane of rotation (head bent forward 30°) the nystagmus is horizontal. Rotatory acceleration also produces head movements and these may actually take the form of head nystagmus. In human beings cessation of rotation may cause turning of the head, body, and arms in the direction of the previously experienced movement, with the result that the individual tends to fall toward that side.

Positional Reflexes.—The tonic labyrinthine reflexes described above are typical of the positional type of response to vestibular stimulation. They act upon all four limbs in the same sense and are readily demonstrated in the decerebrate animal when the influence of the tonic neck reflexes is excluded. The labyrinthine righting reaction, which acts upon the neck muscles to keep the head in a normal position regardless of the position of the body, is another example of this type of reflex. After unilateral labyrinthectomy the asymmetrical elicitation of this reflex from the remaining labyrinth causes a rotation of the head (labyrinthectomized side down) which in turn evokes changes in the trunk and limbs through the tonic neck and neck-righting reflexes. Rolling movements may ensue in the lower animals, but not in man.

The compensatory deviations of the eyes which are evoked by changes in the position of the head are excellent examples of labyrinthine positional reflexes. These reactions can be demonstrated in mammals, but they are most easily studied in certain lower animals, especially in the dogfish. As the head of the fish is slowly turned from side to side, the eyes move so as to compensate for the change in position. On rotating the head to one side, the eye of that side is turned upward, that of the other side downward (Fig. 58, *D*). Appropriate movements of the fins accompany these reactions. In the dogfish the position of the eyes is also controlled by the proprioceptors of the tail muscles, for if the tail is bent from side to side compensating movements of the eyes are produced of the same nature as those which accompany the movements of the tail in swimming (Fig. 58, *B*).

Functional Localization in the Labyrinth.—It has been generally assumed that the acceleratory reflexes arise in the cristae of the semicircular canals, while the positional reflexes have their origin in the otolithic organs (maculae) of saccule and utricle. There is evidence, however, that the matter is not as definite as has been supposed. The original contention of Breuer was that the reflexes obtained by linear acceleration are the only ones of this type which do not depend upon the semicircular canals; he attributed them to the maculae. Magnus and de Kleijn,[171, 172] however, attributed all acceleratory reflexes of labyrinthine origin to the cristae for the reason that they found them intact in guinea pigs which had been subjected to such vigorous centrifuging that all the otoliths had been thrown from the maculae. The fact that these animals showed no positional reflexes whatever lent support to the view that there is a clear differentiation of the receptors of the labyrinth into two groups. But later it was found that the tonic labyrinthine reflexes can be evoked after all the otolithic membranes have been thrown off (de Kleijn and Versteegh[168] and others). This result suggests that at least some of the positional reflexes may

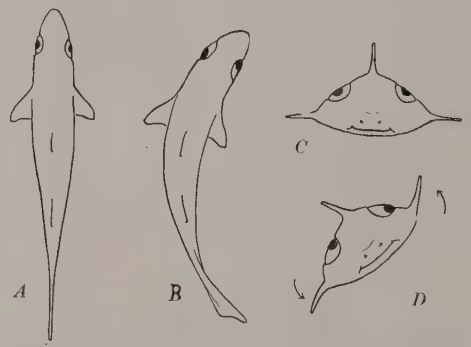

Fig. 58.—Compensatory movements of the eyes and fins of the dogfish. *A* and *C* illustrate the position of the fish when at rest. *B* shows the compensatory movements of the eyes which occur during swimming, or on bending the tail into the position indicated. *D* illustrates the compensatory movements which occur on rotating the fish about its horizontal axis.

be elicitable from the ampullar cristae. Now it has been shown by Versteegh for the rabbit, by McNally for the frog, and by Maxwell for the dogfish that all vestibular responses remain normal after the saccules have been destroyed or denervated. In the light of this fact it is most significant that in the frog Tait and McNally[177] found a perfectly normal righting reflex after section of the nerves to the two utricles. Yet when all labyrinthine receptors except the two utricular maculae were eliminated this response was present though somewhat defective. Tait and McNally have shown clearly that in the frog at least the receptors of the semicircular canals are not stimulated by simple linear acceleration; in these animals the responses to this form of acceleration depend on the utricular maculae. Results of the sort just described show that we must be most cautious in assigning any one function to any individual labyrinthine receptor. Dusser de Barenne[163] has quoted a communication from Versteegh in which this general question is summed up as follows: "We must keep in mind the possibility that the labyrinth functions more as a whole, that all the various reflexes originate in the various receptors,

although perhaps in the normal animal some of the receptors are more important for certain of the reflexes than the others. Thus it would be conceivable that in partial labyrinthine lesions the remaining parts could compensate the functional defects. One would then have to abandon the idea that each subdivision of the labyrinth subserves a special group of labyrinthine reflexes."

The role played by the semicircular canals in the elicitation of responses to rotatory accelerations appears to be obvious from their arrangement in space. This is such as to suggest that the crista of each ampulla is stimulated by rotation of the head in the plane of its canal, probably not at all or very slightly by rotation in any other plane. There is no evidence that the maculae mediate stimulation by rotatory acceleration. The incorrectness of the generally held idea that each canal is responsible for nystagmus in one particular direction should be pointed out. It was shown by de Kleijn and Versteegh[168] that post-rotational nystagmus could be evoked in all three directions in a rabbit after destruction of one entire labyrinth and the ampulla of the posterior canal of the other side. It now seems to be generally agreed that normal stimulation of a crista is effected by currents or displacements of the endolymph which actually move the cupula; and it appears that movement in either direction is an adequate stimulus.

Clinical Tests of the Labyrinthine Mechanism.—The influence of the labyrinth on the postural coordination of the eye and limb muscles, forms the basis for certain useful clinical tests by which the condition of the labyrinth and of its central connections can be determined. These have been developed chiefly by Bárány. In normal individuals when the semicircular canals are stimulated, in addition to the turning sensation and nystagmus, a phenomenon known as *past pointing* occurs. If the subject is directed to close his eyes, extend his arm, raise and then lower it in a vertical plane he will have no difficulty in bringing it back to its original point. If he attempts to do this while the labyrinth is being stimulated he will, if normal, return the arm to a position which deviates from the original point in the direction from which he thinks he is turning, i.e., in the rotation test in the direction toward which he has been spun.

The methods used to excite the canals are called the *rotation test* and the *caloric test.* The former is performed by spinning the subject about two or three times in a pivoted chair, with the head held so that the pair of canals to be tested lie in the plane of rotation. The caloric test depends on the fact that if warm (112° F.) or cold (68° F.) water is poured into the external auditory canal it will set up convection currents in that semicircular canal which lies in a vertical position, and there give rise to excitation. By holding the head in various positions any one of the three canals can be stimulated. The caloric test has the obvious advantage that it excites the canals of one labyrinth only. If labyrinthine stimulation by these methods does not produce after-turning sensations, nystagmus, or past pointing, it is concluded that a lesion occurs in the sense organ or some part of the nervous system involved in the reaction.

CHAPTER XV

THE CEREBELLUM

The cerebellum is a suprasegmental portion of the brain which has developed from the region of termination of the vestibular nerves. In all vertebrates it receives afferent fibers not only from the vestibular nuclei, but also from the spinocerebellar tracts. Since the latter are important pathways for the headward conduction of impulses from the proprioceptors of the body, the cerebellum is obviously a place of convergence of proprioceptive impulses of diverse origins. Taking into consideration this aspect of its organization, Sherrington called the cerebellum the "head ganglion of the proprioceptive system." This designation, however, expresses only one morphological feature of the cerebellum; it is important to understand that in the higher mammals the pontile system of fibers, which transmits impulses from the cerebral cortex, represents the largest afferent connection of the cerebellum.

Inspection of the cerebellum of any of the higher animals reveals a structure of the most puzzling configuration, one in which it is difficult to discern any major subdivisions. And when the student seeks enlightenment in the general literature dealing with this organ he encounters a nomenclature which Riley (see Fulton and Connor[189]) has quite justly described as "fantastic, meaningless and discouraging." Fortunately there has recently emerged from embryological and comparative anatomical studies an interpretation of the cerebellum which creates a degree of order in our conception of the morphology of this part of the brain. This interpretation, which we owe largely to Larsell,[197, 198] provides a solid foundation for investigations of functional localization in the cerebellum and, as Fulton[124] points out, "it now becomes possible more adequately to translate comparative anatomical facts into physiological language." Perhaps the most significant result of this recent integration of morphological and physiological knowledge is the explanation it affords of certain discrepancies which have been noted between the clinical signs and symptoms of cerebellar disturbances in man and the effects of cerebellar ablations in experimental animals. It will doubtless render the results of experimental work more applicable to the solution of clinical problems.

The following account of cerebellar anatomy, taken largely from the writings of Larsell[197, 198] and Fulton,[124, 190] is a necessary introduction to the later discussion of cerebellar functions.

ANATOMICAL CONSIDERATIONS

The gray matter of the adult mammalian cerebellum consists of an outer layer of cortex and a group of nuclei situated in the depths of the organ. With the exception of some vestibular fibers which end in the fastigial nucleus all the afferent fibers entering the cerebellum terminate in the cortex. The greater part of the cortex in turn projects only to the cerebellar nuclei which contain the cell bodies of the neurons whose fibers make up the main efferent channels leading from the cerebellum. Histologically the cerebellar cortex, unlike the cerebral cortex, is of similar structure throughout its vast extent. It thus lacks any

definite cyto-architectonic basis for functional localization. But the developmental history of the cerebellum and the distribution of the terminations of cerebellar afferents of different origins suggest some degree of functional localization within the cortex.

The Morphological Divisions of the Cerebellum

Larsell[197] has shown clearly that the mammalian cerebellum can be divided into two main parts, the *flocculonodular lobe* and the *corpus cerebelli*. These are separated by the *fissura posterolateralis* (Figs. 59 and 60). In adult mammals

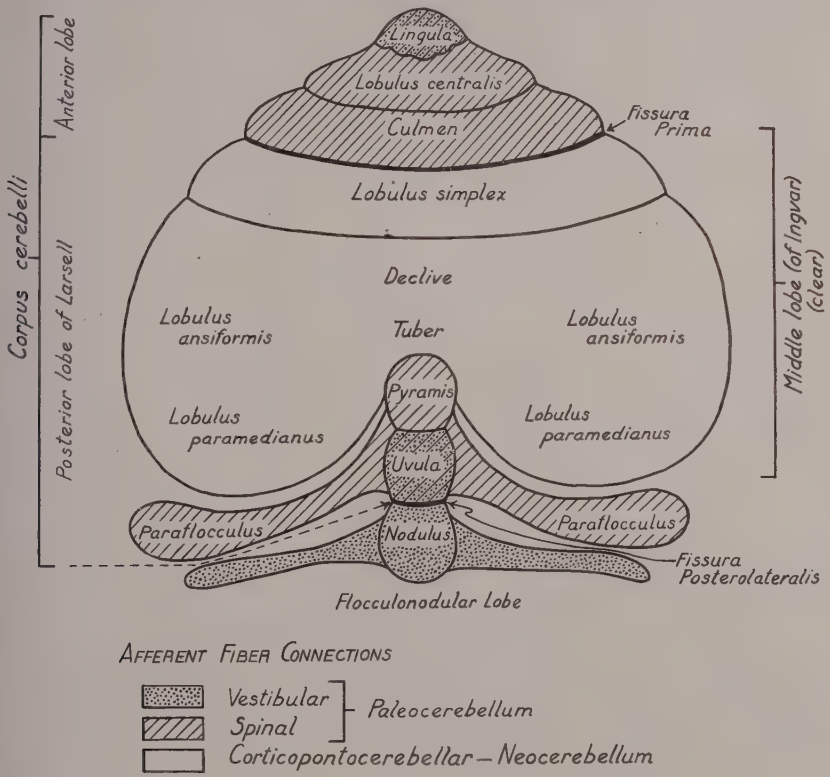

Fig. 59.—Diagram of the cerebellar cortex of the monkey (macaque) to show the principal divisions and afferent connections (after Larsell). The fissura posterolateralis separates the two primary divisions, the flocculonodular lobe and corpus cerebelli. The other features shown in the diagram are discussed in the text. (From Fulton: *Physiology of the Nervous System*, New York, 1938, Oxford University Press.)

the posterolateral fissure is not a prominent landmark, for it has been obscured by the secondary development of cerebellar parts. Nevertheless it is the most fundamental of all the cerebellar fissures; it is the first to appear in the mammalian embryo as well as phylogenetically and in both respects it antedates the much more prominent fissura prima.

The many anatomical facts which have led to this fundamental subdivision have been presented by Larsell.[197, 198] A few of them may be given here in brief outline.

In one of the most primitive vertebrates, the lamprey (Petromyzon), the cerebellum consists essentially of a commissural bridge of fibers of the eighth and fifth cranial nerves which crosses the rostral end of the medulla above the fourth ventricle. It is from this simple structure that the massive cerebellum of higher forms has developed by the migration and proliferation of cells. In higher forms such as the water-living amphibians the development of vestibular and lateral-line systems of nerves is accompanied by an enlargement of the corresponding centers. Those central structures extend forward on each side of the medulla to form the *auricles*. The two auricles are joined by the same commissural bridge (commissura cerebelli) which has been described in the case of Petromyzon, but it now receives a fair number of spinocerebellar fibers in addition to fibers from cranial nerves or their nuclei. But now "accumulations of cells have gathered along the course of the commissures forming two massive nervous structures bounded from each other by the posterolateral fissure. One of these, associated more intimately with the lateral-line and vestibular apparatus, constitutes the lobus auricularis. The other, located between the auricles and having primarily trigeminal and spinocerebellar connections, is the corpus cerebelli" (Larsell and Dow[198]). Compared with the amphibian cerebellum that of the more heavily muscled reptiles has as its chief feature a larger corpus cerebelli. This is doubtless a reflection of the larger number of proprioceptive impulses carried by the spinocerebellar fibers. The vestibular auricular lobe, still separated from the corpus by the posterolateral fissure, is relatively reduced. In the reptiles there are indications of fissures which subdivide the corpus cerebelli.

A key to the interpretation of the morphology of the mammalian cerebellum was found by Larsell in his studies of opossum pouch young. As the organ develops in these primitive mammals, "corpus cerebelli and auricular lobe are shown with almost diagrammatic clarity in various stages of development." *The auricle of lower forms becomes the flocculus of mammals* and a new mass of cortical tissue, the *nodulus*, appears. The nodulus, like the flocculus, has direct connections with the vestibular nuclei and together these structures obviously represent a development in the mammal of the auricles of lower vertebrates. The term *flocculonodular* lobe is therefore substituted for the auricular lobe of submammalian vertebrates. In the adult opossum and in the embryonic stages of all the higher mammals the flocculonodular node is patently distinct from the corpus cerebelli and the posterolateral fissure remains the dividing line.

The Flocculonodular Lobe.—The auricular lobe of the lower vertebrates, from which the flocculonodular lobe of mammals is derived, is largely an outgrowth of the vestibular portion of the medulla and its afferent connections are predominantly with the receptors of the nonauditory labyrinth. The processes of phylogenetic development have evidently not greatly modified the essential features of this primitive arrangement, for the flocculonodular lobe is the only part of the mammalian cerebellum that receives and sends fibers directly to the vestibular nuclei[197, 185] (see Figs. 59 and 60).

The Corpus Cerebelli.—This portion of the cerebellum is by far the largest of the two primary divisions. It is subdivided into an *anterior lobe* and a *posterior lobe* by the *fissura prima*.

The Anterior Lobe.—This is the more primitive part of the corpus cerebelli. Its principal afferent connection is the ventral spinocerebellar tract, although it evidently receives some dorsal spinocerebellar fibers. As indicated in Fig. 59 the lingula probably receives some fibers from the vestibular nuclei.

The Posterior Lobe.—The part of the posterior lobe lying between the fissura prima and the fissure (fissura prepyramidalis) which separates the tuber from the pyramis is sometimes known as the middle lobe of Ingvar (Fig. 59). Larsell[197] prefers to call it the *neocerebellar part of the posterior lobe of the corpus cerebelli*, a designation which emphasizes the functional and developmental sig-

nificance of this region. Its enlargement is the outstanding feature of cerebellar development in mammals; in the higher members of this group its lateral expansion (ansiform and paramedian lobules; cerebellar hemispheres) makes up the greater part of the bulk of the organ. This change is correlated phylogenetically with the development of the cerebral cortex and with the appearance and enlargement of the brachium pontis. The afferent connections of this part are chiefly with the pons and, through the pons, with the cerebral cortex.

The posterior part of the posterior lobe, made up of pyramis, uvula and paraflocculus, resembles the anterior lobe in receiving predominantly spinocerebellar fibers. The uvula also receives some vestibular fibers (Fig. 59).

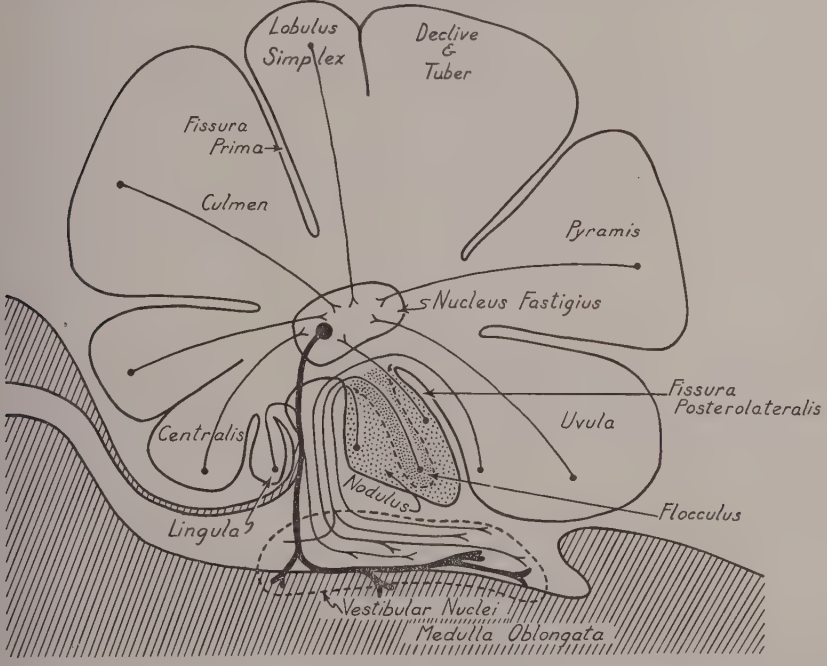

Fig. 60.—Diagram to show the connections from the cerebellar cortex to the fastigial nucleus and to the vestibular nuclei. Corpus cerebelli in white; flocculonodular lobe stippled. Median sagittal plane. (From Fulton: *Physiology of the Nervous System*, New York, 1938, Oxford University Press.)

Anatomical methods of determining the distribution of the terminations of different cerebellar afferents over the cortex have recently been supplemented by physiological means. Dow[187] stimulated the various afferent connections by single shocks and explored the cerebellum with leading-off electrodes to detect the occurrence of electrical responses signalling the arrival of an afferent volley. On stimulation of the eighth nerve the electrical response was limited to the flocculonodular lobe, lingula, uvula, and the fastigial nucleus. Stimulation of spinal nerves or of the spinocerebellar tracts evoked potentials in the anterior lobe, lobulus simplex, pyramis and occasionally in the lobulus paramedianus. When shocks were applied to the pons responses were recorded only from lobulus ansiformis, lobulus paramedianus, declive and tuber, pyramis and paraflocculus; occasionally the culmen, lobulus simplex and pyramis yielded potentials of low amplitude. Curtis[184] employing the same

method, but applying shocks to the cerebral cortex obtained responses in the culmen, lobulus simplex, lobulus ansiformus and lobulus paramedianus, but found the declive and tuber silent. These results in general confirm the anatomical findings.

Neocerebellum and Paleocerebellum.—While there are no sharp boundaries between the various stages of the phylogenetic development of the cerebellum there is a basis for dividing the cerebellum as a whole into older and newer parts. The most distinct phase in the development of the mammalian cerebellum is the latest, namely, the enlargement of the medial lobe of Ingvar, especially its lateral parts. This begins with the definite appearance of the pons and cortico-pontine-cerebellar connections, and it is foreshadowed in certain lateral expansions which occur in reptiles. This general region which receives pontine fibers predominantly can appropriately be called the *neocerebellum*. In contradistinction the rest of the cerebellum being phylogenetically older and receiving chiefly spinal and vestibular afferents may be designated as *paleocerebellum*.

There is even a basis for division into archicerebellum, paleocerebellum and neocerebellum. Thus in the mammalian cortex the flocculonodular lobe, which represents the oldest portion, could be designated as archicerebellar while the somewhat newer paleocerebellar part would include the major part of the anterior lobe and the posterior part of the posterior lobe (uvula, pyramis and paraflocculus). These terms are certainly useful but Larsell[197] points out that there are several degrees of newness in the phylogenetic formation of the cerebellum, and it must be recognized that there are no sharp boundaries between the regions designated.

The division of the mammalian cerebellum into vermis or middle portion and lateral hemispheres has no physiological or comparative anatomical significance. Edinger distinguished a paleocerebellum composed of vermis, flocculus, and paraflocculus from a neocerebellum consisting of the laterally situated hemispheres. But the boundaries set up by such a division separate parts which, as we have seen, are phylogenetically homogeneous. Larsell[197] points out that the vermis is made up of distinct units, some of which are related to the ancient vestibular foundation of the cerebellum (nodulus), others to the spinocerebellar connections (centralis, culmen, pyramis) and still others to the newer cortico-pontine-cerebellar connections (declive, tuber). The emphasis which in the past has been put upon the vermis as a functional entity is misleading.

The Cerebellar Nuclei and the Efferent Cerebellar Projections.—The afferent connections of the cerebellum have been mentioned in connection with the foregoing descriptions of the various subdivisions of the cortex. It may be added here that the fastigial nucleus apparently receives some vestibular afferents. With this exception the cerebellar nuclei appear to receive impulses only from the various parts of the cerebellar cortex (Figs. 60 and 61). They represent the chief source of the fibers which constitute the efferent projections of the cerebellum. It must be realized, however, that in the monkey at least, the flocculus sends all its fibers directly to the vestibular nuclei while the nodulus and uvula send fibers to the medullary nuclei as well as to the fastigial nucleus[185] (Fig. 60).

The efferent connections of the cerebellum provide means whereby this organ can exert effects upon the greater part of the central nervous system. Impulses originating in the cerebellum play directly upon the vestibular nuclei and many other mechanisms of the medulla oblongata, upon the red nuclei of the mesencephalon, and finally upon that part of the thalamus which projects to the

motor areas of the cerebral cortex. Through these connections the cerebellum can indirectly influence most of the other divisions of the neuraxis.

The cerebellar nuclei can be divided into three groups. The *nuclei fastigii,* which occupy the roof of the fourth ventricle (hence the term roof nuclei), constitute the oldest group phylogenetically. As indicated in Fig: 60 they receive fibers from cortical regions which are under the influence of vestibular and spinocerebellar impulses and in which some integration between vestibular and muscular sensibility doubtless takes place. The roof nuclei are thus a place for the further correlation of these influences. Their efferent connections are chiefly through the uncinate fasciculus (hook bundle) which, after looping around the superior peduncle, makes up part of the inferior cerebellar peduncle. These fibers terminate chiefly in the contralateral vestibular nuclei and reticular formation. Thus the origin and the connections of the nuclei fastigii indicate that they are paleocerebellar.

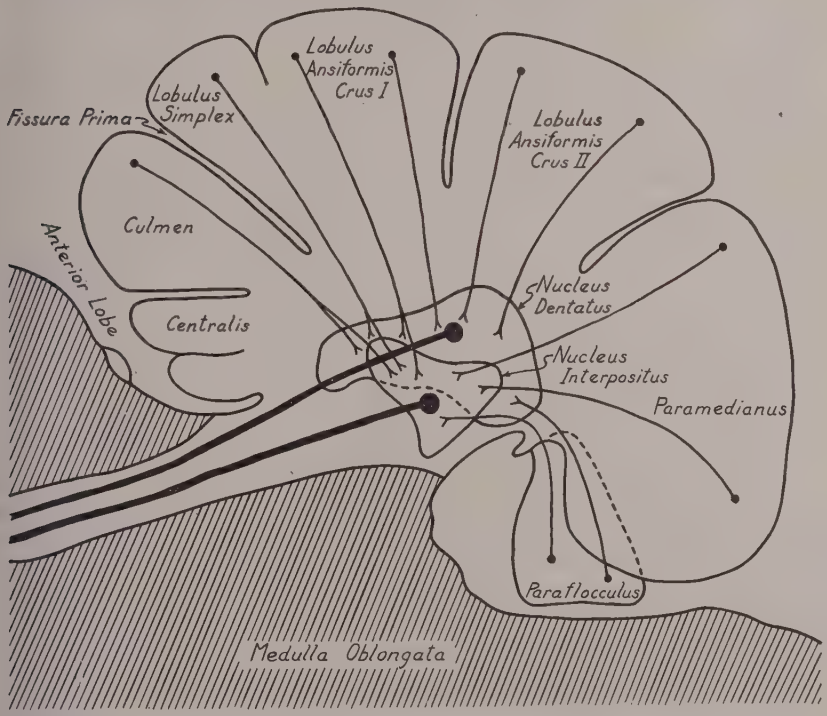

Fig. 61.—Diagram to show the connections of the lateral parts of the corpus cerebelli to the nucleus dentatus and nucleus interpositus. This diagram represents a sagittal section lateral to that represented in Fig. 60. (From Fulton: *Physiology of the Nervous System,* New York, 1938, Oxford University Press.)

In the anthropoids two cellular masses are found lying lateral to the roof nuclei. These are the *nucleus globosus* and the *nucleus emboliformis.* In lower mammals the two are hard to distinguish and for this reason they have been designated as a single complex, the *nucleus interpositus* (Larsell). This concentration of gray matter receives some fibers from the neocerebellar cortex and many from parts of the paleocerebellar cortex which are not entered by direct vestibular fibers (Fig. 61). It is thus a mixed nucleus. It projects by the superior peduncle (brachium conjunctivum) to the large-celled part of the red nucleus which gives rise to the rubrospinal tract.

The *nucleus dentatus,* the most recently developed cerebellar nucleus, is the most lateral. It appears to be the nucleus of the phylogenetically youngest part of the cortex, for it receives many fibers from the lobulus ansiformis and the paramedian lobule. Fibers also reach it from the paraflocculus and anterior lobe, but these probably innervate an anterior portion of the dentate which is related to the medial group of nuclei. The efferent projection of the nucleus dentatus is made up chiefly of fibers which pass via the superior peduncle to the lateroventral nucleus of the thalamus which relays impulses to the motor areas of the cerebral cortex (areas 4 and 6). Only a few fibers of dentate origin terminate in the red nucleus. Clearly this nucleus is predominantly neocerebellar.

EXPERIMENTAL ANALYSIS OF THE FUNCTIONS OF THE CEREBELLUM

Effects of Extirpation

In experimental investigations of the cerebellum the most productive method has proved to be that of extirpation. This is fraught, however, with special difficulty because of the proximity of the important bulbar centers to the field of operation. Erroneous conclusions are very apt to be drawn from the effects of decerebellation when there is failure to distinguish between symptoms of true cerebellar deficit and those which are due to inadvertent injury to the floor of the fourth ventricle. The same mistake is likely to be made in clinical studies of cases of injury or disease of the cerebellum. A cerebellar tumor, for example, may produce many symptoms which are the result of disturbances of bulbar and mesencephalic centers. Another difficulty which has attended every endeavor to establish the functions of the cerebellum has been expressed by Magnus as follows: "Unfortunately we know not a single function or reflex positively connected with the cerebellum, in such way that it is absent after cerebellar extirpation, and present after ablation of other parts of the brain, as long as the cerebellum remains uninjured." *The disturbances created by cerebellar removal or dysfunction are disturbances of postural and phasic activities which are initiated by other parts of the central nervous system.*

Modern studies of cerebellar function had their origin in the extensive investigations of Luciani[199] who was the first to study long-surviving decerebellate mammals (dogs). According to Luciani three stages may be distinguished in the appearance of the symptoms following removal of the entire cerebellum. The first period, roughly ten days in duration, is one of "functional exaltation" in which the animal exhibits tonic extensor rigidity, especially in the forelegs, opisthotonos and clonic spasms of the hind legs. This group of "dynamic phenomena" is presumably due to certain immediate effects of the operation. After a week or more these effects change quite completely and "deficiency phenomena," which are the permanent results of the loss of cerebellar tissue, present themselves. Luciani recognized at this stage a triad of symptoms which he regarded as primarily expressive of absence of cerebellar function: (a) *asthenia,* or general muscular weakness, affecting the hind legs more than the forelegs; (b) *atonia,* or, more correctly, hypotonia, a less than normal tonus of the body musculature, which is most pronounced in the hind legs; (c) *astasia,* or irregularity of muscular contraction, which is seen particularly in movements of "voluntary" type and is the basis of the so-called "intention tremors." Finally, a certain improvement in the behavior of the animal occurs. Luciani attributed this to the compensatory action of other parts of the brain which modify their activities so as to correct for the loss of cerebellar influences. This final stage, the period of "compensation," is marked by increasingly successful attempts to stand and walk. Complete recovery was never observed by Luciani, nor has it ever occurred in any of the decerebellate preparations of other workers.

Luciani also studied the effects of unilateral extirpation of the cerebellum. The general result was the same as that which ensued upon complete removal, but the symptoms were

always confined to the muscles of the same side of the body. All subsequent workers have confirmed Luciani's conclusion that each lateral half of the cerebellum exerts an influence which is strictly ipsilateral.

Recent experiments on the removal of the cerebellum in animals by Dusser de Barenne[188] and others have shown that the asthenia and hypotonia observed by Luciani in his decerebellate dogs and emphasized in the general literature on this subject are not due to the loss of cerebellar tissue but to injury of the underlying vestibular nuclei. It is now an established fact that when the cerebellum is successfully removed from a dog without secondary injury to the floor of the fourth ventricle no muscular weakness or diminished tone can be detected. The period of dynamic phenomena (opisthotonos, head retraction, extensor spasm of forelegs, clonic spasms of the hind legs) was found by Dusser de Barenne to pass gradually into a period of compensation during which the animal becomes able to right itself, stand, and walk. Marked tremor and dysmetria, or an apparent misjudgment of distances in the execution of motor acts, characterize every effort of the decerebellate animal to regain or maintain these positions.

Fig. 62.—Exaggeration of the *magnet reaction* (exteroceptive component of the positive supporting reaction) in a decerebellate dog. When the animal is suspended with feet free (*A*) the back is concave and the legs show moderate flexion. A light touch applied to the ventral surface of one hind foot (*B*) causes the legs to become rigid pillars in a position of extreme extension, and simultaneously the back is straightened by contraction of the dorsal muscles. (From Rademaker: Das Stehen, Berlin, 1931, J. Springer.)

The earliest attempts at progression result in jerky movements of the hind legs which merely push the animal along on its extended forelegs. Later, when walking and running become possible, the gait is markedly ataxic. Nystagmus, widely regarded as symptomatic of cerebellar deficiency, does not appear unless the vestibular nuclei have been injured. Flexor withdrawal of a leg, scratching and other movements, which are essentially spinal reflexes, do not exhibit any abnormalities, and certain more complex acts, such as licking the coat, are carried out smoothly in normal fashion. There are no signs of muscular weakness; Rademaker has shown that a decerebellate dog is able to run, carrying on its back a load equal to its body weight. It has often been claimed that the cerebellum is an organ of equilibrium, but actual experiment shows that in its absence the righting reactions are so pronounced that it is extremely difficult to force the animal to lose its equilibrium. No labyrinthine reaction is abolished and the animal promptly corrects any passively induced abnormal position of its legs. On the basis of the experiments of Dusser de Barenne and Rademaker it has

become apparent that the most significant result of decerebellation is a disturbance in the control of certain complex movements which is expressed in the form of *tremor, dysmetria, asynergia,* and *ataxia.* All subsequent workers have confirmed Luciani's finding that after unilateral decerebellation the disorders are confined to the musculature of the ipsilateral half of the body.

The terms by which the various signs and symptoms of cerebellar deficit are described are often employed loosely and with various connotations. Unless they are used with discrimination these rather imposing words of classical derivation are apt to serve merely as a means of conveying the vaguest of impressions. The student should know just what they do mean. Walker and Botterell[202] and Fulton and Dow[190] (see also Fulton[124]), following the conventions adopted by Holmes,[194] have given the following clear definitions:

Cerebellar ataxia is a term used to embrace all abnormal motor phenomena of cerebellar deficiency, including dysmetria, tremor, decomposition of movement, etc. (Since "ataxia" may be confused with locomotor ataxia caused by destruction of the dorsal roots, Fulton prefers the term *asynergia* which has the advantage that it implies inharmonious action of synergic muscle groups.)

Dysmetria is taken to include any disturbance in the range of voluntary movements.

Hypermetria is excessive range of movement as when the limb overshoots the desired point.

Hypometria is deficient range of movement so that the limb stops before the goal is reached.

Decomposition of movement represents the performance of an act so that "the various components of the act are not performed in their proper sequence."[194]

Tremor may be classified as that occurring in an extremity at rest or maintaining a posture ("static tremor"), and that occurring during any part of active movement ("kinetic tremor"), and in any plane. Terminal tremor, i.e., the tremor occurring at the end of a movement is usually more marked than the tremor at the start or during the course of a movement.

Tone is applied by the clinician (Holmes[194]) "to that slight constant tension characteristic of healthy muscles, owing to which the limbs, when handled or moved passively, offer a definite resistance to displacement." This definition is somewhat less precise than that of the physiologist who looks upon tone as a reflex postural contraction due to the stretch reflex or to motor discharges of low frequency set up by a number of influences (see Chapter XIV).

"Hypotonia" is a somewhat unsatisfactory but widely used term denoting a diminished resistance to passive movement; the passive movement of a hypotonic limb may be carried through a range greater than normal, and on passively shaking the proximal segment of a "hypotonic" limb there is abnormal excursion at the affected joint.

A very thorough analysis by Rademaker[175] of the effects of decerebellation has explained some of the disorders of posture and movement in terms of disturbances of certain specific reactions. The decerebellate dog stands as if on stilts with back convex instead of straight or slightly concave; the legs are hyperextended and abnormally abducted so as to afford a wide base for the support

of the body. This peculiar stance, which is one of the most characteristic abnormalities of the animal without cerebellum, is the result of an overactive positive supporting reaction in which the extensors and abductors play more prominent parts than under normal circumstances. The exaggeration of the positive supporting reaction is particularly well seen when it is elicited with

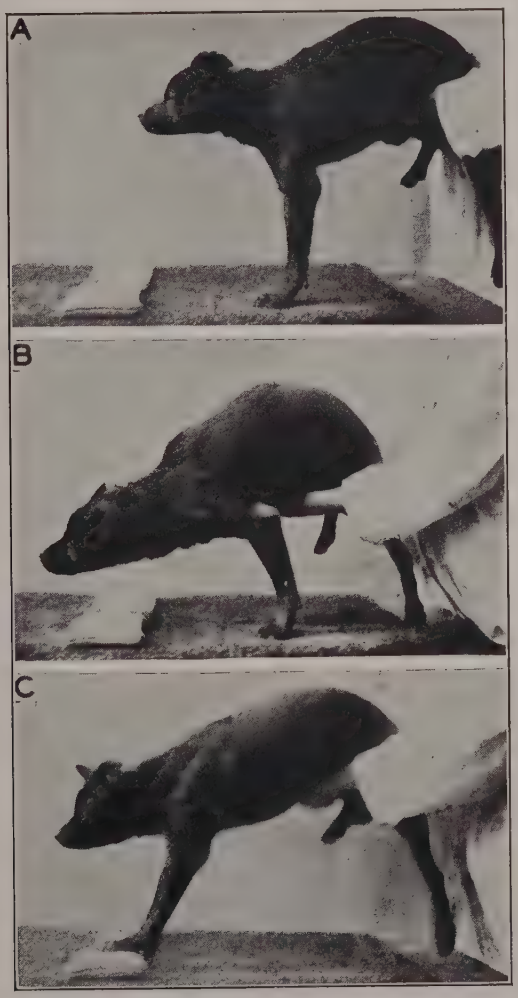

Fig. 63.—Abnormal hopping reaction in a decerebellate dog. *A*, *B*, and *C* are frames from a motion picture film. In *A* the animal is allowed to stand on one foreleg; it shows a marked supporting tone (overactive positive supporting reaction). On forward displacement of the body (*B*) the leg fails to hop despite considerable retroflexion at the shoulder. Finally, after still further displacement, hopping occurs, but the movement is hypermetric and as a result the animal comes to a standing position in which the foot is too far advanced (*C*). (From Rademaker: Das Stehen, Berlin, 1931, J. Springer.)

the animal held suspended in the air. Fig. 62 shows that the exteroceptive component of this response, the magnet reaction, which normally is not very pronounced, becomes, after decerebellation, so great that it affects not only the legs but also the back and neck. We have already seen that in the normal animal stretching the flexors of the distal joints is the most important factor in evoking the reaction. Rademaker has shown that other reactions in response to stretch are modified by decerebellation. The hopping reactions (see page 141), which act to maintain equilibrium when the body is moved in the horizontal plane, are likewise overactive, but they are at the same time retarded, so that displacement of the body to one side is compensated for by a movement of the leg which begins late and is hypermetric (Fig. 63). Hypermetria resulting from the exaggerated execution of a movement is a general phenomenon in decerebellate preparations. For example, in eating, the mouth is opened too widely, and in stepping, the feet are lifted too high. Excess contraction of this sort in agonists tends to evoke abnormally vigorous stretch responses in antagonists, and Rademaker has suggested that tremor may be explained on such a basis. The righting reactions are so overactive that in recovering its normal position the animal rotates its head or body too far, but this leads to an exaggerated "rebound" in the opposite direction with the result that it makes several oscillatory movements before coming to rest in the proper posture. Rademaker's analysis has made possible the first satisfactory description of the nature of cerebellar ataxia. In walking or running an exaggerated and abnormal positive supporting reaction resulting in excessive extension and abduction of the leg is induced by each contact of a foot with the ground. For this reason decerebellate animals tend to go forward in zigzag fashion, swinging from side to side. At each step the foot is lifted abnormally high and the attitudinal responses to change in the position of the head are brusque and excessive. Horizontal displacement of the body is thus constantly threatening equilibrium. Although able to maintain the animal in the upright posture, the hopping reactions are retarded and hypermetric and so add further to the disturbance of the gait. It is easy to understand how this combination of abnormally executed reactions results in ataxia.

When the cerebellum is completely removed in a monkey, without any injury to underlying structures, the result is similar to that described by Luciani for the dog.[180] Extensor spasm and opisthotonus during the early postoperative stages are, however, not marked. The animal is incapacitated for some time; it is unable to sit up for about two weeks. "After six weeks it is able to walk unsupported, but exhibits wild ataxia in all movements frequently striking its face with its hand when feeding."[190] A gross tremor appears when the animal first attempts to make "volitional" movements, and this disorder continues as an outstanding feature of the animal's motor deficiencies. The positive supporting reaction may be increased, but this postural adjustment apparently never exhibits the low threshold and overaction characteristic of its elicitation in the decerebellate dog. Further, there may be some hypotonia.

It is important to bear in mind that the abnormalities which follow removal of the cerebellum result from abnormal functioning in the remaining parts of the central nervous system. Ablation of the cerebellum withdraws regulatory influences from many central nervous mechanisms. Even the

"dynamic phenomena" which characterize the freshly decerebellate state probably represent release of function rather than stimulation resulting from the immediate effects of the operative procedure. The condition of extensor spasm with opisthotonos closely resembles decerebrate rigidity, which, as we have seen, is a release phenomenon; it is too long continued to be the result of irritation. Indeed if the cerebellum or only its anterior lobe be removed in a decerebrate cat or dog the extensor rigidity is markedly augmented and the head is kept dorsiflexed in typical opisthotonus. Furthermore, it is well known that in cats and dogs electrical stimulation of the anterior surface of the vermis and other parts of the cortex inhibits the "decerebrate" rigidity produced by transection above the level of the red nuclei. The cerebellum thus exerts, through its efferent fibers, an inhibitory influence on extensor tonus. The permanent abnormalities of decerebellate preparations, the tremors, dysmetria, asynergia, and ataxia, result from disturbances in the execution of many responses which are essentially dependent on the remaining parts of the brain. The cerebellum plays an active role in modifying the activities of the centers which have to do with the supporting, righting, hopping, and other postural reactions, but it is not an essential part of the nervous mechanisms involved in these responses.

The tremor which is seen in patients with cerebellar tumors or injuries is confined to voluntary movements. This fact suggests that in the absence of the cerebellum the cerebral cortex is unable normally to effect the acts for which it is necessary. In a study of decerebellate cats Fulton, Liddel, and Rioch[191] showed that no tremor occurs until the animal attempts to move "voluntarily" and that subsequent removal of the cerebral cortex abolishes the tremor which had characterized the previous "voluntary" movements of the animal. They suggest that cerebellar tremor may be due to incomplete compensation on the part of the cerebral cortex for the loss of the cerebellum. More recently Aring and Fulton[180] have extended this study to monkeys and baboons. In the primate the greater differentiation of the cerebral cortex makes it easier to determine experimentally just which portion may be involved in the production of the tremor. It was found that the tremor and dysmetria which develop in the ipsilateral half of the body after unilateral decerebellation are abolished temporarily and depressed permanently by ablation of the contralateral motor area (area 4). On the other hand, removal of the premotor area (upper part of area 6) markedly accentuates the cerebellar symptoms and permanently impairs the animal's capacity to compensate for a cerebellar deficit. The conclusion drawn is that the premotor region plays an important part in the compensation which normally follows removal of the cerebellum.

The Effects of Regional Destruction and Stimulation: Functional Localization in the Cerebellum

The effects of cerebellar ablations which we have described indicate that the two halves of the cerebellum are each concerned with adjustments of tone and movement in the corresponding half of the body. Beyond that they do not afford any evidence of localization of function in the cerebellum.

In discussing the problem of localization in the central nervous system one must distinguish between the representation and control of a discrete part of the body in a specific part of the central organ and a delimitation of the central management of some general function. The cerebral cortex displays the first

type of localization rather conspicuously, but it is also organized on the basis of the second. Much debate has taken place regarding localization of function in the cerebellum. By studying the correlation between the functional importance of different muscle groups and the development of the several divisions of the cerebellum Bolk assigned the control of each muscle group to a definite part of the cerebellar cortex. For example, finding that the lobulus simplex is unusually well developed in the giraffe he inferred that it is concerned with the regulation of the neck muscles. Bolk's interpretation of his comparative studies has received some support from certain experimental investigations. But this concept has been in sharp conflict with the view that the cerebellum "functions as a whole" (Luciani; Sherrington). Recently acquired experimental evidence indicates that neither of these extreme views is correct. The cerebellum exhibits functional localization in the sense that each of its major subdivisions exerts different effects upon the control of movement and posture by the rest of the central nervous system. It does not appear to be organized on the basis of a narrowly delimited control of separate anatomical entities. The evidence supporting this interpretation has been derived chiefly from investigations of the functions of three parts of the cerebellum: the flocculonodular lobe, the anterior lobe, and the neocerebellar portion of the corpus cerebelli.

The Flocculonodular Lobe.—Anatomical considerations strongly suggest that this most primitive part of the cerebellar cortex has vestibular functions. Dow[186] has obtained physiological evidence that this is the case in experiments performed on monkeys and a few higher primates. Excision of the nodulus, with or without removal or injury of the uvula, caused a disorder of equilibration characterized by falling, oscillations of the head, a peculiar staggering gait (titubation) and "ataxia of the trunk." These symptoms are pronounced for a time, but improvement begins early and leads to complete or nearly complete recovery. The vestibular nature of the disorder is demonstrated by the fact that it was not produced by nodular removal if the animal had been recently deprived of vestibular function by bilateral labyrinthectomy. Dow suggests that the syndrome represents a kind of "hypermetria" of certain vestibular functions. It is significant that no comparable disturbance is created by lesions of other parts of the cerebellar cortex and that the nodular syndrome does not include changes in the positive supporting reaction and the righting reactions.

The Anterior Lobe.—The relation of this part of the corpus cerebelli to the control of muscle tone has already been mentioned. Physiologists have paid it especial attention for the reason that in all vertebrates it is electrically excitable. Bremer[182] has shown that its stimulation in birds (pigeon) causes marked ipsilateral inhibition and contralateral excitation of extensor responses followed by a rebound consisting of augmentation of extension ipsilaterally and inhibition contralaterally. The same effects are seen in the cat and dog. Evidently this region contains mechanisms for regulating extensor tone. The inhibitory influence seems to be predominant, for removal of the lobe augments the positive supporting reactions and, when it is done in a decerebrate cat or dog preparation, greatly increases the hypertonia of the antigravity muscles. Recently Fulton and Connor[189] have reported results which show that in the monkey the anterior lobe subserves similar functions; its removal in these primates causes "conspicuous disturbances in the postural sphere, increased

tendon reflexes, pronounced lengthening and shortening reactions and gross exaggeration of positive supporting reactions."

The Neocerebellum.—It cannot too strongly be emphasized that the great development of the neocerebellar portion of the corpus cerebelli is the chief distinguishing feature of the cerebella of the higher mammals. Since this development is correlated phylogenetically with the development of the cerebral cortex and because the connections of this region are, on the afferent side, with the pons, and on the efferent with the thalamus (through the dentate nuclei), we may suppose that it represents a huge chain of internuncial neurons (see page 102) which are set into action by impulses in the cortico-pontine-cerebellar systems of fibers and which in turn modify the corticobulbar and corticospinal mechanisms. Physiological evidence supporting this idea is available. We have seen that stimulation of the pons (Dow[187]) or motor cortex (Curtis[184]) is followed by cerebellar electrical responses which are confined to the neocerebellar regions. Rossi first showed that stimulation of the ansiform lobule increases the excitability of the motor area of the opposite cerebral hemisphere. More recently Walker[201] has demonstrated that the spontaneous electrical activity (see page 238) of this part of the cortex is markedly increased by contralateral cerebellar stimulation; the effect is mainly obtainable from the neocerebellar parts and it cannot be elicited after section of the superior cerebellar peduncle. It should be recalled that the fibers of the brachia conjunctiva decussate.

Ablation of the neocerebellar cortex in cats and dogs results in surprisingly slight and transient effects. Bremer[182] has reported the occurrence of tremor and hypermetria, but Keller, Roy and Chase[196] found that partial and complete removals of this part of the cerebellum in dogs and monkeys lead to no detectable dysfunction. Botterell and Fulton,[181] however, found more definite disturbances in primates. When bilateral ablations were restricted to neocerebellar cortex and white matter, they caused awkwardness in volitional movements, hypotonia, fatigability of the muscles, disturbances in gait "characterized by leaping and an inability to arrest forward progression when an obstruction is in view." Tremor occurs for only a day or two. When the ablations include the dentate nuclei, all the symptoms are exaggerated and tremor is more enduring. Unilateral removals produce only ipsilateral disturbances. The effects of small lesions are not restricted to any one group of muscles. Recovery is extensive after both unilateral and bilateral extirpations: "at the end of six weeks animals having such lesions cannot be distinguished from normal by ordinary tests." Hypotonia seems to be the most persistent result. Evidently in the carnivores and the lower primates other parts of the brain, presumably the motor areas of the cerebral cortex, can compensate almost completely for the withdrawal of neocerebellar influences. That this is not the case in the higher primates is shown by the persistence of the symptoms which follow injuries of the cerebellar hemispheres in chimpanzees and man.

The Cerebellar Nuclei.—Little is known of the nature of the part played by these structures in the fashioning of cerebellar influences. We have just seen, however, that the dentate nuclei apparently make an independent contribution to the sum total of the effects exerted by the neocerebellum. Stimulation of the other nuclei produces changes which are striking and similar to those which occur on electrical excitation of the anterior lobe.[192, 193, 200] They are changes in posture which develop rather slowly and result in a definite pattern of

attitudes. One of the most striking features of these responses is the rebound which follows cessation of the stimulus; a posture develops which is just the opposite of that produced during the excitation. But these responses do not seem to be peculiar to the nuclei, since Clark[183] has obtained similar ones from stimulation of the cerebellar cortex in unanesthetized cats.

EVIDENCE OF THE NATURE OF CEREBELLAR FUNCTIONS FROM CLINICAL STUDIES

Cerebellar disorders in man are caused by injuries, tumors, and vascular accidents. It is generally agreed that hypotonia and asthenia (muscular weakness) are prominent symptoms of cerebellar disease. In this respect the clinical picture contrasts sharply with that seen in the dog and other lower mammals after decerebellation. These animals show weakness and subnormal muscle tone only when in the course of the operation the vestibular nuclei have been injured. But well-marked hypotonia was almost always found in those cases of gunshot wounds of the cerebellum, studied by Gordon Holmes,[194] in which there was little reason for supposing that the floor of the fourth ventricle was involved. An explanation of this difference is afforded by the results of the comparative physiological studies outlined above. In the laboratory carnivores, hypertonia in the form of augmented positive supporting reactions rather than hypotonia follows complete removal of the cerebellum. In the monkey complete removal may be followed by some degree of hypotonia and the positive supporting reaction is not greatly enhanced. But when the anterior lobe alone is removed, the postural status of a monkey closely resembles that of one of Rademaker's wholly decerebellate dogs (Figs. 62 and 63). Now neocerebellar removal, which has little if any effect on muscle tone in carnivores, produces hypotonia in primates and to an extent which corresponds to their position on the phylogenetic ladder. Thus it is evident that within the range of experimental animals hypertonia gives way to hypotonia as a symptom of complete decerebellation when the neocerebellum reaches a certain stage of development. In man the neocerebellar portions of the corpus cerebelli, because of their size and position, are the parts most commonly involved in cerebellar injury or disease. Presumably if the anterior lobe is involved, the effect is overshadowed by that of the neocerebellar deficiency. But of this we cannot be certain; few if any cases of lesions restricted to the anterior lobe have been reported in the clinical literature. Holmes[195] points out that in man the paleocerebellum is a relatively insignificant part of the whole and we know little of its functional capacities.

Except for the symptoms of hypotonia and asthenia, the clinical and experimental studies of cerebellar function have yielded results which are in substantial agreement. The deficiency phenomena and the process of compensation which follow war wounds of the cerebellum have been exhaustively described by Gordon Holmes.[194] When the injury is restricted to one lateral half of the cerebellum, the abnormalities of muscular action are confined to the same side of the body and may be conveniently compared with the normal acts carried out by the muscles of the unaffected side. Perhaps the most pronounced symptom is *intention tremor,* which affects voluntary movements and is more marked the more strongly willed the movement. Under *asynergia* may be classed irregularities in the execution of complex movements which are carried

out by the synchronous adjustment of the activities of cooperating muscle groups. When, for example, the fingers are flexed, the extensors of the wrist normally contract synergically in order to prevent simultaneous flexion of the wrist. If a patient with a cerebellar lesion grasps a small object quickly, the wrist may be extended excessively so that the hand is bent backward before the fingers are half flexed. Movements which involve the activities of several joints are frequently *decomposed* into their component parts which are executed one at a time, as if "by the count," instead of all at once. In bringing the finger to the nose the patient will first depress the shoulder, and then flex the elbow after the first act is complete. Difficulty is also experienced in making rapid alternate movements, such as pronation and supination of the arm. To this abnormality Babinski gave the name *adiadochokinesis*. Another prominent symptom is *dysmetria*, which is especially marked when an attempt is made to perform some precise movement. The finger may strike the eye, when its true objective is the mouth. It is impossible to stop the movement at the right point, with the result that in trying to reach some object, the hand strikes it forcibly or passes beyond it. In walking, the cerebellar patient, like the decerebellate dog, may reel drunkenly, and it is not uncommon for him to be mistaken for a case of alcoholic intoxication. The *ataxia* is an expression of the asynergic and dysmetric contraction of the muscles used in standing and walking.

From his very great experience with the symptoms resulting from lesions of the human cerebellum Holmes[195] concludes that the essential disturbances are: "(1) postural hypotonia and impairment of certain reactions of the toneless muscles; (2) mild degrees of asthenia and fatigability of the muscles; (3) abnormalities in the rate, regularity and force of voluntary movements, and (4) failure of certain associated movements.

Lesions of the corpus cerebelli in man, according to Holmes, never produce symptoms limited to one part of the body. If an arm is affected, the leg of the same side shows corresponding disorders. The evidence from human material appears on the whole to be in accord with the more trustworthy of the experimental results in indicating that the cerebellum is not organized to exert isolated control of specific parts of the body musculature, but acts to influence in several ways general postural and motor functions.

This concept of cerebellar localization of function is borne out by the occurrence in man of what appears to be a syndrome of destruction of the flocculonodular lobe. This condition is encountered in children who are the victims of a malignant tumor, the medulloblastoma, which arising above the fourth ventricle, often apparently in the nodulus itself, tends to destroy selectively, in the early stages of its growth, the basal midline portions of the cerebellum.[124] These cases may therefore, for a time at least, be comparable to Dow's monkeys in which the nodulus was removed surgically. The syndrome seen in children thus afflicted has been described by Fulton as follows: "The child becomes unsteady on its feet, progresses with a broad base, often losing its balance and falling backwards. There is conspicuously little tremor of the extremities, and if the patient lies in bed with his trunk at rest there may be no trace of cerebellar incoördination in his arms or legs." The syndrome is essentially a disorder of equilibration and is quite distinct from that which results from neocerebellar lesions; it is very similar to the one produced in monkeys by lesions restricted to the nodulus (see page 160).

No Sensory Disturbances Follow Injury to the Cerebellum.—In considering the function of the cerebellum it should be pointed out that although it receives afferent impulses from the proprioceptors of the body, there is no evidence that it is concerned in any way with sensation. The only sensory tests to which those afflicted with cerebellar injuries fail to respond with normal accuracy are those involving the comparison of weights placed in the normal and the affected hand. In this test the weight in the latter is judged heavier than it should be because of the greater effort required to support it with the asthenic and tremorous muscles. Although the ability to maintain the equilibrium of the body may be disturbed as the result of cerebellar injury, this is because the muscles do not respond properly in the attempt to prevent falling, and not because the *sense* of equilibrium is in any way impaired.

CHAPTER XVI

THE AUTONOMIC NERVOUS SYSTEM, OR THE EFFERENT PATHWAY TO VISCERAL EFFECTORS

The motor neurons that connect the central nervous system with skeletal muscle fibers have their cell bodies in the brain stem or spinal cord; one nerve cell bridges the gap between cerebrospinal axis and effector organ. The innervation of the visceral effectors (secreting cells, smooth muscle, and cardiac muscle) is arranged in a somewhat different manner. It is characterized by the fact that the axons which come into immediate functional relation with these effector cells belong to neurons that lie entirely outside the central nervous system. The cell bodies of these outlying neurons are typically grouped together in *peripheral ganglia.* There they make synaptic connections with axons arising in the central nervous system. The breaking of the path from central axis to effector by a peripheral synapse is a distinctive feature of the motor innervation of the viscera. This arrangement is illustrated in Fig. 64 which represents the essential difference between the somatic and visceral motor paths. In the case of the visceral nerves the neuron on the central side of the peripheral synapse is called *preganglionic,* that on the distal side *postganglionic.* Embryological studies have shown that the postganglionic neurons originate as neuroblasts within the neural tube and, early in the course of development, migrate outward to take their characteristic peripheral positions. They are thus the homologues of the motor neurons of the somatic or cerebrospinal system, while the preganglionic neurons have their counterparts in the centrally placed premotor neurons of that system. In Fig. 64 this homology is illustrated by the use of broken lines.

One other morphological feature distinguishes the visceral from the somatic innervation. While the cerebrospinal fibers pass out from the brain stem and spinal cord in an almost unbroken series, the preganglionic fibers issue in three distinct groups, as was first shown by Gaskell.[220] The first of these, the *cranial* outflow, is composed of visceral motor fibers in the third, seventh, ninth, and tenth pairs of cranial nerves. The fibers of the second division arise from all the thoracic and from the upper three, four, or five lumbar segments of the spinal cord and begin their peripheral course in the ventral roots of the corresponding spinal nerves; they form the *thoracolumbar* outflow. The third division, the *sacral* outflow consists of fibers which originate from the second, third, and fourth sacral spinal segments. Visceral fibers do not issue in some of the cranial nerves, and the cervical and lower lumbar segments do not contribute to the preganglionic outflow (see Fig. 65).

The entire visceral innervation, postganglionic neurons and ganglia as well as preganglionic neurons, may be separated into cranial (mesencephalic-bulbar), thoracolumbar, and sacral divisions. The terminology that has grown up in connection with these three divisions is confusing. Each has been given several names and different authors have applied the same name to different divisions. The entire system of visceral nerves was called by Langley,[226] to whom we owe

much of our knowledge of these structures, the *autonomic nervous system.* He used the ancient name "sympathetic" for the thoracolumbar division and classed the cranial and sacral divisions together under the term *parasympathetic.* The word *sympathetic* has been applied to each and all of the three divisions, but was originally introduced in 1732 by Winslow to describe the chain of ganglia and associated strands which we now know to be connected with the thoracic and upper lumbar segments of the spinal cord. Accordingly, Langley's use of the term has a historical justification. Since the cranial and sacral divisions possess certain common features which distinguish them from the middle division, they are conveniently described together as the parasympathetic system. Langley's terminology is the one most frequently encountered in current physiological literature and for that reason it will be followed in the present treatment of the subject. In Table II it may be compared with those used by several other writers.

TABLE II

TERMINOLOGY OF LANGLEY	SYNONYMS		
	(GASKELL)	(MEYER)	(L. R. MÜLLER)
AUTONOMIC NERVOUS SYSTEM	INVOLUNTARY NERVOUS SYSTEM	VEGETATIVE NERVOUS SYSTEM	VEGETATIVE NERVOUS SYSTEM
1. Sympathetic (thoracolumbar autonomic)	1. Sympathetic	1. Sympathetic	1. Sympathetic
2. Parasympathetic (tectal and bulbo-sacral autonomic)	2. Enteral	2. Autonomic	2. Parasympathetic

It should be pointed out that all these terms, Langley's included, are inappropriate. For example, it is misleading to emphasize the fact that the motor nerves to visceral effectors subserve involuntary functions, for much of the activity of the somatic motor nerves supplying skeletal muscle is equally involuntary. The word "vegetative" suggests a nonspecific control of growth and metabolism that is not in keeping with the established functions of this system of nerves. Again, the term "sympathetic," which had its origin in the ancient belief that the "sympathies" of the body are mediated through the various connections of the outlying ganglia, has lost its significance in the face of modern knowledge. Finally, the adjective "autonomic" implies a functional independence of the system that is nonexistent, for the normal activity of these efferent neurons is dependent upon their central connections. Langley was, indeed, aware of this fact when he proposed the term. His investigations had, however, led to new conceptions that made it desirable to introduce a fresh term for the system in question. It is easy to agree with his explanatory statement that "it is more important that new words should be used for new ideas than that the words should be accurately descriptive." Certainly the terms of other writers possess no advantage as descriptive terms over those of Langley. Although his terminology leaves much to be desired, there can be no question of the fitness of the suggestion made by Schilf that the term "autonomic nervous system" ought to be used in recognition of Langley's great contribution to our knowledge of the nervous organization in question.

While details of the anatomical course of the fibers to the great variety of structures innervated by the autonomic system are beyond the scope of a textbook of physiology, it will be necessary to outline certain generalities concerning the arrangement of the preganglionic and postganglionic neurons. But first of all it may be pointed out that, in addition to the obvious methods of tracing the paths of nerve fibers by degeneration and by stimulating the roots of motor nerves, knowledge of the distribution of preganglionic neurons has been gained by the use of a special method discovered by Langley and Dickinson in 1889. This depends on the fact that nicotine in certain concentrations specifically blocks the passage of nerve impulses across synapses between preganglionic and postganglionic neurons without disturbing conduction in nerve fibers uninterrupted by a synapse. Consequently, when nicotine

is painted upon an outlying ganglion it is possible to determine, by stimulating the preganglionic fibers, whether they pass through the ganglion without interruption or not. In this way it has been learned that the motor paths in the autonomic system fall into three groups with regard to the position of the synapse between the preganglionic and the postganglionic neuron.

THE SYMPATHETIC DIVISION OF THE AUTONOMIC SYSTEM

Anatomical Organization.—The preganglionic fibers of this division have their cell bodies in the region of the lateral horns of the gray matter of the thoracic and upper lumbar spinal segments. Emerging in the ventral roots with the motor fibers supplying skeletal muscle, they leave the spinal nerves to form the white rami communicantes and course to the ganglia of the sympathetic system (see Fig. 64). These ganglia fall into two distinct groups.

The *lateral* (or *vertebral*) *ganglia* are arranged in two chains lying along the ventrolateral aspects of the vertebral column and extending from the upper cervical region to the coccyx (Fig. 65). The ganglia of each chain are connected by longitudinal fibers. In general these ganglia have a segmental arrangement, but in the cervical and upper thoracic regions several have fused to form the stellate, inferior cervical, and superior cervical ganglia. One characteristic of the lateral ganglia is that they send postganglionic fibers to the spinal nerves. These fibers form the gray rami communicantes. Gray rami contribute fibers to every spinal nerve while white rami issue only from the thoracic and upper lumbar ventral roots. Each spinal nerve thus conveys sympathetic postganglionic fibers to the blood vessels of skin and skeletal muscle, to the sweat glands, and to the smooth muscles of the hairs. Postganglionic fibers from the superior cervical ganglia are distributed to the smooth muscle of the orbit and to the glands and blood vessels of the cranial region. The upper cervical spinal nerves receive their gray rami from these same ganglia while the inferior cervical ganglion supplies gray rami to the lower cervical nerves. From some of the lateral ganglia, notably those of the upper thorax, postganglionic fibers run directly to the viscus innervated.

The *collateral* (or *prevertebral*) *ganglia* are the ganglia of the so-called solar plexus (the semilunar and superior mesenteric ganglia), the inferior mesenteric ganglia, and some small nearby ganglia. They lie near the points of origin of the main arteries supplying the abdominal viscera. From them postganglionic fibers course with the arteries to innervate the abdominal viscera and their blood vessels. These ganglia receive preganglionic fibers through white rami from the fourth or fifth thoracic to the second lumbar nerves. In this case the preganglionic fibers join the lateral chain, but continue to the collateral ganglia as the *splanchnic nerves.*

The fibers of the sympathetic system have a very wide distribution throughout the body. They include: vasoconstrictor and some vasodilator fibers to the small blood vessels; accelerator fibers to the heart; secretory fibers to the sweat glands; inhibitory and motor fibers to the smooth muscle of the gastrointestinal tract; motor fibers to the smooth muscle of the hairs; constrictor fibers to the spleen; dilator fibers to the bronchioles and coronary vessels; cervical sympathetic fibers to the eyes causing dilatation of the pupils, retraction of the nictitating membranes (where these are developed), and projection of the eye forward in the orbit (exophthalmos); fibers to the pelvic viscera, and finally secretory fibers to the medullary portion of the adrenal glands.

The innervation of the adrenal medulla is peculiar, for the secretory cells of this endocrine organ receive preganglionic fibers directly from the splanchnic nerves. This apparent exception to the rule that organs innervated by the autonomic system receive postganglionic fibers is explained by the fact that the secreting cell of the adrenal medulla is the morphological homologue of the postganglionic sympathetic neuron. In the embryo both types of cells arise from a common central mass, and in certain lower vertebrates they have a common peripheral distribution. It is not surprising, therefore, that the secretion of these glandular cells, adrenalin, when circulating in the blood stream, acts upon any tissue in the same way as do nerve impulses conducted by sympathetic

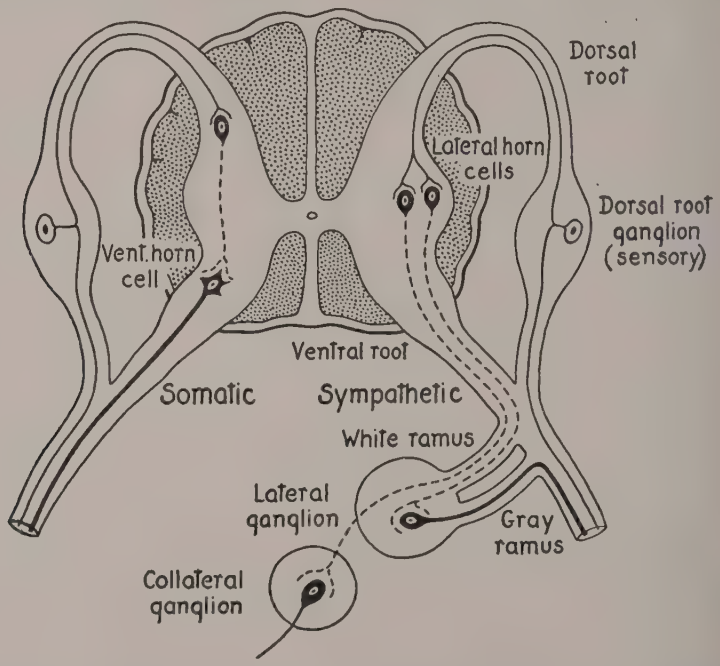

Fig. 64.—Diagram illustrating the different arrangements of neurons in the somatic and autonomic nervous systems. At left is shown a single spinal reflex arc of the somatic system, at right that of the sympathetic division of the autonomic system. At right, the preganglionic neurons are represented by broken lines, the postganglionic by solid lines. (After Gaskell.)

postganglionic fibers (Elliott). *These facts show that the adrenal medulla is in effect an integral part of the sympathetic system.* The latter may indeed be called, with perfect propriety, the *sympatho-adrenal system.*

Cannon[208] has pointed out that besides the *extensiveness* of the distribution of its fibers another important feature of the sympathetic system is its arrangement for a *diffuse* discharge of nerve impulses. It was found by Langley that the preganglionic fibers forming any one white ramus pass to a series of lateral ganglia, usually from six to nine in number, never to a single segmental ganglion. He also obtained evidence that any one preganglionic fiber may send collaterals to make synaptic connections with postganglionic neurons in several ganglia.

Obviously postganglionic neurons outnumber preganglionic neurons. The exact ratio for the entire sympathetic system is not known, but in the case of the superior cervical sympathetic ganglion of the cat each preganglionic fiber innervates, on the average, thirty-two postganglionic neurons (Billingsley and Ranson). Thus the morphological arrangements are such that widespread changes in effectors must occur when any fraction of the preganglionic outflow is active. Furthermore, a discharge of nerve impulses over that single group of preganglionic fibers which innervates the adrenal medulla will throw into the blood stream a humoral agent capable of inducing almost every one of the changes which result when the entire thoracolumbar outflow discharges.* These facts lead plainly to the conclusion that the sympathetic division of the autonomic is in general organized to *act as a whole.*

Functions of the Sympathetic System.—This portion of the autonomic system has many duties in the animal economy, but details of the processes which it controls must be sought in other sections of this book. Only a summary of these together with an interpretation of the general functions of the system will be given in this chapter.

A large fraction of the preganglionic outflow is constantly discharging nerve impulses and this so-called "tonic" activity is responsible for a number of sustained bodily conditions. A continuous activity of the widely distributed vasoconstrictor fibers keeps the smooth muscle of the arterioles in a state of tonic contraction, a peripheral condition of major importance in the maintenance of an adequate arterial pressure. The pulse rate tends to remain relatively rapid because of the tonic discharge of the cardio-accelerator fibers. Section of the cervical sympathetic trunk leads not only to vasodilatation in the head region, but also results in constriction of the pupil, enophthalmos, and, in animals which possess an active nictitating membrane, passive projection of that structure over the front of the eye. These tonic sympathetic discharges are of central origin, and they may be decreased by inhibition or augmented by excitation of the central neural mechanisms in control of the preganglionic neurons (see Fig. 185, p. 465). It has been shown that the potential waves signalling these persistent discharges in postganglionic sympathetic fibers are irregular and wax and wane with the respiratory movements and the heartbeat (see Fig. 131, p. 372). Because of the sluggish response of smooth muscle this fluctuation is smoothed out when it is translated into tonic contraction (see Figs. 169 and 170). Certain sympathetic paths, namely, those to the gastrointestinal musculature, to the sweat glands and smooth muscle of the hairs (pilomotors), and to the adrenal medulla, appear to be usually at rest, and they become active only when special conditions lead to excitation of their central connections.

It is true that one or more functional groups of sympathetic fibers may be affected without involvement of other groups. A lowered arterial pressure may lead to compensatory augmented activity of the vasoconstrictor and cardio-accelerator mechanisms without obvious extension of the response to other parts of the sympathetic system. Several examples of such fractional activity in the sympathetic might be described. Without doubt, however, the most significant aspect of the physiology of this system is its tendency to go into action

*Although the sweat glands have a sympathetic innervation, they are not affected by adrenalin. It is also true that the response of the pilomotor muscles to adrenalin is negligible. These are the only exceptions to the well-established principle that adrenalin has a general sympathomimetic action.

as a whole. Consideration of the bodily changes evoked by unitary activity of the sympathetic shows them to be related in such a way that they cooperate to mobilize energy and to provide for its ready utilization. Energy transformation in the body involves oxidation of foodstuffs with the production of carbon dioxide, other metabolites, and heat. Its principal seat is the skeletal musculature. When it is augmented, the active tissues demand more oxygen, more food material, and the means of disposing of additional quantities of metabolites and heat. Normally these requirements are met by prompt internal responses. Sympathetic discharge is the immediate cause of many of them. By accelerating the heart and by causing vasoconstriction in quiescent regions (especially the splanchnic area), it tends to increase the flow of blood through the active tissues. It thus provides a means of supplying extra oxygen and additional sources of energy to the site of augmented metabolism and of removing metabolites and heat. At the same time that there is a shunting of blood to the active organs from the splanchnic area gastrointestinal functions, temporarily unnecessary, are inhibited by sympathetic impulses. The discharge further facilitates the respiratory processes by dilating the bronchioles and by increasing the number of circulating red corpuscles through its action on the smooth muscle of the spleen. As the result of their action on the sweat glands sympathetic impulses provide for loss of excessive amounts of heat. There is also evidence that the sympathetic supply to skeletal muscles acts there to reduce or delay the peripheral processes of fatigue.[87] Circulating adrenalin, itself discharged by sympathetic impulses, not only supplements the effects of impulses in postganglionic sympathetic fibers generally, but appears to be the most potent agency for rapid mobilization of blood glucose. In addition, this hormone has the property of hastening the coagulation of blood.

Cannon[208] has pointed out that the conditions under which the sympathetic actually does discharge vigorously as a unit are those which require an energetic response to insure the maintenance of an essential bodily state or even of life itself. Such conditions include strong muscular exercise, asphyxia and anoxemia, pain, emotional excitement, hypoglycemia, and exposure to cold. From the account just given it can be seen that in muscular activity a diffuse and widespread discharge of sympathetic impulses would go far toward mobilizing bodily resources. Since pain, asphyxiation, oxygen-lack, exposure to cold, and strong emotions, such as rage and fear, are likely to be accompanied or followed by muscular effort, the visceral changes evoked by sympathetic activity are appropriate and quite necessary in those states. When the warm-blooded animal is exposed to a lowered environmental temperature, increased activity of the skeletal musculature in the form of restlessness and shivering produces additional quantities of heat. Of importance in preventing the threatened depression of body temperature are visceral changes induced by sympathetic discharge. There is the same mobilization of energy that occurs in muscular exercise; furthermore, constriction of peripheral vessels and erection of hair or feathers reduces the loss of heat from the body surface. Secretion of adrenalin also occurs under these circumstances, and it results in an acceleration of oxidative processes. Indeed there is evidence to indicate that this event represents the first line of defense against a falling blood temperature, for animals with denervated adrenals shiver sooner and more vigorously than do normal animals when exposed to cold.[213] The blood sugar, like the blood temperature, is kept at a rather constant

level. When the normal amount is greatly diminished, as by an excessive dose of insulin, hypoglycemic reactions occur. These vary from species to species and include signs of sympathetic discharge. It has been shown that the hypoglycemic state is accompanied by secretion of adrenalin and that this is of sufficient magnitude to check the rate of fall of the glycemic percentage.[211]

In each of the states of physiological stress that have been outlined, widespread sympathetic discharge leads to changes that anticipate or ameliorate the danger. This fact, the realization of which is due to the work of Cannon, has been described by him as the *emergency function of the sympatho-adrenal system.* Already it has been pointed out that the adrenal medulla is in reality a part of the sympathetic system. Although this organ of internal secretion can be stimulated directly by severe asphyxia, the physiological circumstances that throw it into action do so by provoking a discharge in the secretory fibers that reach it through the splanchnic nerves. A considerable mass of evidence is at hand to show that neither this innervation nor the cells of the adrenal medulla are tonically active.[209] Such evidence as has been put forward (Stewart and Rogoff) in favor of continuous secretion was obtained under such disturbing experimental conditions as trauma and anesthesia. In his studies of this question Cannon used surviving unanesthetized animals whose hearts, sensitized by denervation, would respond by acceleration to 1 part of adrenalin in 1,400,000,000 parts of blood. He was unable to find any noteworthy differences between the basal heart rates before and after inactivation of the adrenal medulla. On the other hand, despite a number of reports to the contrary, it now appears to be fully established that medulliadrenal secretion occurs as a part of the sympathetic activity that is induced by the various emergency states described above.

No better confirmation of the validity of the emergency theory of sympathetic functions could be desired than the demonstration of the effects of surgical exclusion of sympathetic nerve impulses. Cannon and his collaborators[212] have removed from animals both sympathetic chains from the superior cervical to the pelvic ganglia. Such a procedure entirely disconnects all sympathetically innervated effectors from the central nervous system and removes through degeneration all postganglionic fibers except those originating in the collateral ganglia. No more pronounced effects were produced when, in addition, the semilunar ganglia, one adrenal gland, and the medulla of the other, were extirpated. The sympathectomized animals continued to live for many months without apparent difficulty. The operations invariably failed to produce striking alterations in the body. There was an almost negligible reduction of the basal metabolic rate. When young kittens were unilaterally sympathectomized and allowed to mature, the skeleton and viscera of the two sides showed equal and normal growth. It has been made clear that totally sympathectomized cats continue to live without difficulty, free from functional deficiencies, so long as they are not subjected to conditions of physiological stress. When they exhibit anger or fear, they do not show the bodily changes which constitute the necessary visceral support for the muscular activity of attack or escape. Sympathectomized cats are also defective when exposed to cold. They are unable to check heat loss through cutaneous vasoconstriction and pilomotor activity. In winter the sympathectomized animal, therefore, exhibits an increased tendency to remain near sources of heat, and when exposed to low temperatures, it

suffers a depression of body temperature not seen in the normal animal. This defect is associated with exaggerated shivering, a compensation that doubtless prevents grave hypothermia. It has also been demonstrated that after extirpation of the sympathetic chains, cats show deficiencies in their ability to withstand hemorrhage, anoxemia, and hypoglycemia (Sawyer and Schlossberg). Denervation or removal of the adrenal medulla apparently produces the same hypersensitivity to insulin as does complete sympathectomy, and this fact emphasizes the special service of adrenalin in combating this emergency state (see Chapter LI).

The earlier experiments involving complete sympathectomy were carried out chiefly on cats. Later it was found by Brouha, Cannon and Dill[207] that the ability of dogs to engage in vigorous muscular exercise is not impaired by sympathectomy. On the other hand, Hodes[224] showed conclusively that sympathectomized cats display a diminished capacity for muscular exercise. This difference led McDonough[228] to compare sympathectomized and normal dogs in regard to their ability to withstand other critical situations. She found that the former exhibit essentially normal ability to withstand exposure to heat and cold and oxygen lack. But the results showed that the sympatho-adrenal system is as important in the dog as in the cat in protecting the organism against insulin hypoglycemia. McDonough attributes the remarkable ability of sympathectomized dogs, as compared with sympathectomized cats, to endure unfavorable environmental conditions to "numerous accessory physiological devices, not under sympathetic control, that are possessed by the dog as a running animal: larger lungs and heart per kilogram of body weight, greater blood volume, higher hemoglobin content, abundant salivary flow and a long tongue for heat loss, and a common resort to shivering for heat production." She points out that these devices are unavailing in insulin hypoglycemia and for this reason the effects are the same as in the cat.

There is another way of characterizing the experimental facts that have just been reviewed. Claude Bernard, and after him several other physiologists, emphasized the fact that an essential condition for the normal existence of the higher animals is the constancy of the conditions immediately surrounding the tissue cells. This point has been elaborated by Cannon,[210] and he has suggested the term "homeostasis" to describe the steady state of the *milieu interne*. His review of the physiological reactions which assure homeostasis shows that a considerable number of them involve the sympathetic system. Indeed it is clear that this nervous apparatus is of the greatest importance in preserving homeostasis during grave crises. For this reason the middle division of the autonomic may be looked upon as the special and immediate agency of homeostasis.

THE PARASYMPATHETIC DIVISION OF THE AUTONOMIC SYSTEM

This part of the autonomic, formed by classifying together the cranial and sacral divisions, is composed of fibers that carry nerve impulses to many organs situated in diverse parts of the body. The third cranial nerves supply visceral motor fibers to the ciliary muscle and the sphincter of the pupil. The seventh and ninth pairs distribute secretory and vasodilator impulses to the salivary glands and the mucous membranes of the buccal region. The vagi furnish inhibitory fibers to the myocardium, constrictor fibers to the bronchioles, vasoconstrictor fibers to the coronary vessels, and motor and secretory fibers to the musculature and glands of the gastrointestinal tract as far distally as the ileocolic valve. Turning to the sacral outflow we find the pelvic nerves, the so-called nervi erigentes, composed of fibers that cause increased motor activities in colon, rectum, and bladder, and vasodilatation in the external genitalia.

In the variety of its distribution and in the number of effects which it evokes, the parasympathetic resembles the sympathetic. Indeed, a majority of the viscera is innervated by both divisions of the autonomic. There is, however, an important difference between the organizations of the two systems. The

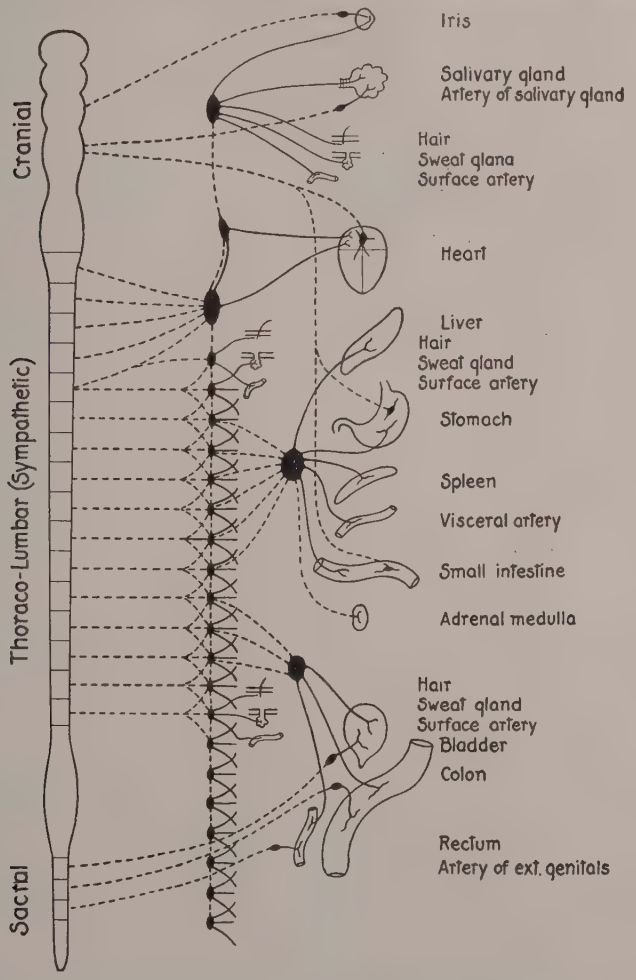

Fig. 65.—Diagram of the general arrangement of the autonomic nervous system. The brain and spinal cord are represented at left. The nerves of the somatic system are not shown. The preganglionic fibers are in broken lines. The postganglionic in solid lines. For further description see text. (From Bard after Cannon: *The Foundations of Experimental Psychology.* Clark Univ. Press.)

most significant morphological fact about the parasympathetic is that groups of preganglionic fibers reach out to ganglia which lie within or close to the organ innervated. Mention may be made of the ciliary, submaxillary, cardiac, and

intrapulmonary ganglia. There is good reason to believe that the ganglion cells found in the myenteric and submucous plexuses belong to the parasympathetic innervation of the gastrointestinal tract. The postganglionic fibers issuing from any one of these ganglia are short and supply a circumscribed mass of tissue (Fig. 65). This *restricted distribution* is an arrangement that makes it possible for the central nervous system to exert effects upon a single organ without at the same time affecting other organs. It is this feature that distinguishes the parasympathetic most sharply from the sympathetic in which the neural arrangements are such as to favor the production of widespread simultaneous changes.

The characteristic anatomical organization of the parasympathetic is correlated with absence of unitary action in this system. Should this division go vigorously into action as a whole, there would be produced widespread coincident changes bearing no functional relation to one another; the result would be disorderly and purposeless. Constriction of the pupil, slowing of the heart, increased gastrointestinal activity, contraction of bladder and rectum, and engorgement of erectile tissue are not responses that are bound by any physiological ties of integration. It is not surprising therefore that the adrenal medulla has no counterpart in the parasympathetic system and that no parasympathomimetic hormone capable of acting extensively upon organs innervated by this system is liberated in the body.

Despite the lack of functional interrelation between the several groups of parasympathetic fibers, it is possible to describe in a general way the respective functions of the cranial and sacral divisions. Cannon has characterized the former as a group of efferent paths devoted to the protection and conservation of bodily resources. The tonic activity of the cardio-inhibitory fibers under normal conditions and their reflexly augmented discharge when the heart is overtaxed by a high arterial pressure protect that organ from overactivity. Similarly, constriction of the pupil by reflex activation of third nerve fibers protects the retina from excessive light and even under ordinary intensities of illumination a tonic discharge of these parasympathetic neurons is a necessary condition for acute vision. The conserving function of the cranial autonomic is perhaps best illustrated by its control of digestive processes. The secretory fibers of the seventh and ninth nerves are responsible for the discharge of saliva. This secretion facilitates mastication and swallowing and initiates the hydrolysis of carbohydrate. Vagal fibers are concerned in the secretion of the gastric and pancreatic juices, and they promote the tone, rhythmic activities, and peristalsis of esophagus, stomach, and small intestine. Obviously the cranial parasympathetic contributes in a very definite manner to the nutrition of the body. For this reason it is an important factor in homeostasis. Its service in maintaining the constancy of the internal environment is, however, far more indirect than that of the sympathetic division which acts directly and promptly to prevent disturbing alterations in blood and tissue fluids.

The sacral autonomic has been characterized as a group of neural mechanisms for emptying. The contractions of bladder, colon, and rectum which lead to their evacuation are parasympathetic reflexes for which the adequate stimulus is distention by accumulation of contents. Defecation and micturition are, however, processes which may be prevented or facilitated by the contraction of skeletal muscle, and it should be recognized that much of the activity of the sacral autonomic involves the cooperation of the cerebrospinal nervous system. It is

notorious that bladder and rectum may be emptied quite involuntarily during strong emotional excitement, and under such circumstances sacral autonomic discharges occur concomitantly with vigorous sympathetic activity. The rhythmic contractions that empty the vasa deferentia and seminal vesicles at the height of sexual excitement in the male and the supposedly analogous contractions of the uterus that are said to coincide with orgasm in the female are not due to sacral discharges, for these organs are supplied chiefly, if not solely, by sympathetic fibers. The usual forerunner of these events is, however, a sacral vasodilator discharge to the external genitalia and in the male it is commonly provoked by distention of tubes and vesicles.

It has long been recognized that stimulation of the peripheral stump of a cut dorsal root will cause vasodilatation in the area supplied by the corresponding spinal nerve. Bayliss advanced the opinion that the fibers concerned in this phenomenon are not true efferent nerve components, but are in fact ordinary sensory fibers that send collaterals to peripheral vessels and are therefore capable of inducing a vascular effect when they conduct antidromically, i.e., outward instead of inward. Although there can be no doubt that certain dorsal root fibers do mediate vasodilator impulses, there is still no agreement as to the true nature of these fibers. A few investigators hold that they are efferent fibers whose cell bodies lie within the spinal cord. Ken Kuré places them among a large group of efferent posterior root fibers which he claims to have identified and which he classifies as parasympathetic. Kuré's contention has not escaped serious criticism and it remains to be determined whether the posterior roots actually give rise to a functionally important group of visceral efferent fibers. There is, however, good evidence that in mammals the cell bodies of all dorsal root fibers are in or near the ganglia of the root (Hinsey;[128] Westbrook and Tower[153]). Whatever may be the nature of the dorsal root fibers which mediate vasodilatation, there is no good reason to extend the term "parasympathetic" to include them.

THE ANTAGONISM OF THE TWO DIVISIONS OF THE AUTONOMIC SYSTEM

The sweat glands, the pilomotor muscles, the smooth muscle of the nictitating membrane, the blood vessels of the digestive tract between mouth and rectum and of the glands opening into that portion, receive autonomic fibers only from the sympathetic system. Most of the visceral tissues, however, possess a double nerve supply, sympathetic and cranial or sympathetic and sacral. Wherever this occurs, the sympathetic and parasympathetic as a rule exert opposed effects. In the heart the sympathetic exerts a positive, the cranial a negative influence upon excitability, conduction, and frequency and strength of the beats. In general, it can be said that the sympathetic sends inhibitory fibers to the smooth muscle of the entire gastrointestinal tract except the sphincters. The parasympathetic, on the other hand, supplies motor fibers to the stomach and small intestine by way of the vagi and to the colon and rectum through the sacral outflow. The cranial innervation of the eye contracts the pupil, the sympathetic dilates it. While the parasympathetic sends vasodilator fibers to the brain, salivary glands, and external genitalia, these parts, in common with tissues generally, receive a vasoconstrictor supply from the sympathetic.

The opposition of the effects of the sympathetic and parasympathetic innervations is the basis of certain reciprocal relationships between them. In many visceral organs the same effector cells receive inhibitory fibers from one division of the autonomic and excitatory fibers from the other. Where this occurs, as in the heart (see Fig. 127) and certain parts of the vascular bed,

the two sets of fibers act in a reciprocal manner upon a single effector. Cardiac acceleration occurring as a result of reflex stimulation or during muscular exercise is the outcome of lessened vagal tone and greater accelerator discharge. This is a special kind of reciprocal innervation in which only the organization of the central neural mechanism is the same as in the control of antagonistic skeletal muscles. The difference between the two cases is that the autonomic arrangement involves an inhibitory nerve to the periphery and an effector common to both innervations.

THE GENERAL NATURE OF AUTONOMIC CONTROL

When we examine the contribution which the autonomic system makes to the organization of bodily processes, we are struck by the fact that these nerves regulate the activity of a group of organs and tissues which possess a high degree of autonomy, so that their various functions can be carried out, to a considerable extent at least, when they are completely isolated from the central nervous system. The dispensability of the sympathetic division has already been noted. Although completely parasympathectomized animals have not been prepared, the results of section of certain large fractions of the preganglionic outflow of this division are well known. Evidence is thus available to show that in general the autonomic system exerts a regulatory rather than an essential influence upon the viscera. The heart is perhaps the most complex organ under autonomic control, yet not only will isolated strips of this organ contract in the rhythmic fashion characteristic of the heart's activity, but the entire organ will beat in a perfectly coordinated way when freed from all connections with the central nervous system. The sustained contraction of the musculature of the arterioles, essential to the maintenance of arterial pressure, is greatly diminished by cutting the sympathetic vasoconstrictor fibers, but it soon returns as a result of the development of an intrinsic tone. Although temporarily paralyzed by double vagotomy, the smooth musculature of the distal esophagus, the stomach, and small intestine is able to resume its normal tone and to show normal peristalsis and rhythmic activity after complete severance of its extrinsic nerve supply. While the "psychic secretion" of gastric juice is no longer possible after section of the vagi, the secretion of gastric, pancreatic, and intestinal juices which occurs in response to the presence of food in the stomach and duodenum is brought about largely by hormones, so that nerves are unnecessary for this activity. Section of the sacral autonomic nerves leads to a severe paralysis of the urinary bladder, and although emptying never becomes adequate, some return of function actually does occur (see Chapter LXXXIII).

Such facts raise the question of the source of the activity of visceral effectors whose extrinsic nerves have been cut or extirpated. Two answers have been given. The tendency of earlier physiologists was to attribute the independent activity to intrinsic neurons that remain in many viscera after severance and degeneration of the extrinsic fibers and which usually cannot be removed without profoundly disturbing the effector cells themselves. This explanation implies a neurogenic source of the activity, but in the case of the heart, the blood vessels, the uterus, and the intestine, recent work favors a myogenic explanation. Whether the peripheral plexuses of vertebrates represent something akin to the nerve nets of the lower invertebrates is a question that remains unanswered.

Visceral afferents do not belong to the autonomic system. Strictly speaking, the autonomic system is made up entirely of motor nerves. Although afferent

fibers connected with sense organs situated in visceral tissues course in many autonomic nerve trunks and strands, they have their cell bodies in the sensory ganglia of the cranial and spinal nerves and so belong to the somatic system rather than to the autonomic. These neurons should not be termed autonomic afferents. Centripetal discharges in most of them reflexly evoke changes in skeletal muscle as well as in visceral effectors.

Langley was unable to obtain any experimental evidence that true reflexes are mediated through autonomic ganglia and convincing evidence for any such arrangement is still lacking.

A type of reflex which may operate here is that known as the *axon reflex*. The only axon reflex which is known to function, except under laboratory conditions of stimulation, affects the cutaneous blood vessels. This reaction was first postulated by A. N. Bruce as a result of his studies of the inflammation induced by mustard oil. The vascular dilatation set up by this irritant was shown to persist after cutting the sensory roots of the nerves supplying the region of application, and consequently could not be attributed to a reflex involving the central nervous system. After the sensory fibers had degenerated, however, the effect could no longer be elicited. Furthermore, the induction of local anesthesia by cocaine or novocaine before the application of mustard oil proved to be equally effective in preventing the vasodilatation. It appears, therefore, that the reaction depends on the integrity of the peripheral end of the sensory fibers. It is believed that these send off collaterals which connect with the cutaneous capillaries and arterioles and subserve a vasodilator function. Centripetal impulses set up by the irritant in the sensory termination will, on passing up the fiber, spread along all its branches and so cause relaxation of the small blood vessels innervated by the vasodilator collateral. This mechanism may explain the observation of Bayliss, already mentioned, that stimulation of the peripheral stump of the dorsal root of a spinal nerve causes a local vasodilatation in the skin area supplied by that nerve. A similar axon reflex evocable in certain sympathetic preganglionic fibers was investigated by Langley and Anderson. The fibers in question pass down the hypogastric nerves to aberrant ganglia located distally to the inferior mesenteric, but they send collaterals to make synaptic connections with postganglionic fibers which arise in this ganglion and pass down the other hypogastric nerve. When one hypogastric nerve is cut, stimulation of its central stump produces, on the opposite side, contraction of the bladder and internal anal sphincter, and pallor of the rectum. Since application of nicotine to the inferior mesenteric ganglion abolishes this effect, it must be due to spread of antidromic impulses set up in the preganglionic fibers along their collaterals which connect with postganglionic neurons whose fibers course down the opposite hypogastric nerve. There is no evidence, however, that this type of mechanism is ever brought into play in normal life.

THE CHEMICAL MEDIATION OF AUTONOMIC NERVE IMPULSES

Vertebrate skeletal muscle does not receive an inhibitory nerve supply and in this respect differs sharply from many visceral effectors. One of the outstanding characteristics of the autonomic system is the fact that many of its postganglionic fibers exert inhibitory effects. The problem of the nature of inhibition in its various guises has been prominent in physiology ever since the discovery in 1845 by the Weber brothers, of the cardio-inhibitory function of the vagus nerves. Little is known concerning the intimate nature of inhibition, but it can be said that an important step forward was made in 1921 when Otto Loewi[227] demonstrated that Ringer's solution in contact with a frog heart which has been slowed or stopped by vagal stimulation, takes on the property of being able to induce typical vagal effects in a second heart. This result led him to conclude that vagal impulses act on the heart through the production of a chemical agent which he designated "vagus substance." Loewi also found that stimulation of the accelerators of his preparation caused the bathing solution to become capable

of exerting typical sympathetic effects on another heart. In the course of the last decade Loewi's results have been decisively confirmed by a number of investigators.

The contributions of Loewi not only elucidated the problem of inhibition but initiated a series of investigations which have shown that in mammals as well as in cold-blooded vertebrates impulses carried by autonomic fibers exert their effects through the agency of specific chemical substances. This whole subject has been reviewed by Cannon and Rosenblueth to whose monograph[214] the reader is referred for a full account of the evidence put forward up to 1937.

The Mediator of Parasympathetic Postganglionic Impulses.—The term "vagus substance," first used by Loewi to denote the active material liberated in the heart on vagal stimulation, is not sufficiently broad. Subsequent work has made it clear that this agent is produced wherever parasympathetic impulses reach an effector organ, and that it acts on any other similarly innervated tissue in the same way (producing excitation or inhibition) as does that tissue's parasympathetic nerve supply. Thus a perfusate which has passed through the vessels of the tongue while they are actively dilated as a result of stimulation of the parasympathetic vasodilator fibers in the lingual nerve has a typical vagal effect on the muscle of the intestine (Bain). Also, it has been shown that Locke's solution which has passed through the vessels of the cat's submaxillary gland during periods of excitation of the chorda tympani nerve will inhibit the isolated frog's heart, increase the tone of a strip of rabbit's intestine, cause a fall in blood pressure and provoke salivary secretion (Gibbs and Szelöczey[221]). Further advances were made possible when it was found that the substance liberated in the frog's heart on parasympathetic stimulation (1) has the properties of an ester of choline, (2) is rapidly destroyed by an esterase present in blood and all tissues and (3) is protected from the action of the esterase by the drug *eserine* (physostigmine). Eserine has proved most useful in the study of this subject, for it permits the easy detection of the presence of the mediator in blood or perfusates. After injecting eserine it is possible to demonstrate the liberation of the mediator on stimulation of the parasympathetic nerve to one organ by the appearance of typical parasympathetic effects in some distant organ. The drug, however, has been used most often to protect the mediator in perfusion fluids or blood which are tested on various biological preparations after passage through the organ in which it is suspected that the mediator is being produced (see Fig. 66).

The identity of the parasympathetic mediator with *acetylcholine* is now generally recognized and admitted. In 1914 Dale showed that acetylcholine when injected into the blood stream of a mammal reproduces the effects of stimulating parasympathetic nerves. The resemblance is comparable to that between the actions of adrenalin and the effects of sympathetic nerves. In their physiological actions the mediator and acetylcholine are identical; both are rapidly destroyed by blood or tissue esterase, and the breakdown of both by blood or tissue extracts is checked by eserine, which in turn, as has long been known, prolongs and potentiates the effects of parasympathetic nerve stimulation. Acetylcholine is the only ester of choline which has been identified in animal tissues. Particularly significant is the fact, shown by Dale and Feldberg,[210] that when a sample of venous blood or perfusate containing the active substance

is compared with a dilute solution of acetylcholine, the two exhibit a constant quantitative relation in their effects on various indicators (Fig. 66).

A pharmacological fact of some significance in this connection is that *atropine* prevents the inhibitory action of vagal stimulation on the heart. This drug also blocks many other parasympathetic effects. The action resembles that of curare in blocking the transmission of excitation between a cerebrospinal nerve and skeletal muscle. Loewi and Navratil have shown that atropine does not interfere with the production of the vagomimetic substance in the heart, but somehow prevents it from acting on the effector cells.[214] Atropine also prevents many of the actions of acetylcholine.

The most sensitive test-object for demonstrating the presence of acetylcholine is a strip of the longitudinal body muscle of the leech. After being prepared, cleaned and soaked in a weak solution of eserine, it becomes sensitized and then contracts when brought into contact with as little as 0.002 mg. of acetylcholine per liter of solution. In order of sensitiveness, other biological test-objects are: isolated and eserinized rabbit auricle; isolated

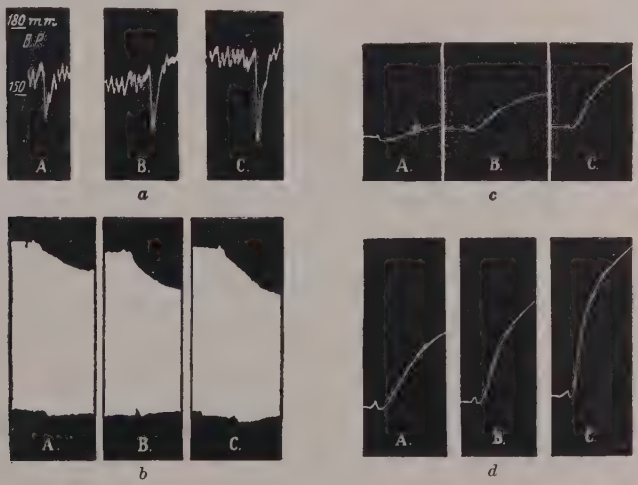

Fig. 66.—Tests of a concentrated perfusate of eserinized Locke's solution which passed through the blood vessels of the stomach of a dog during vagal stimulation. Before stimulation the perfusate was little, if at all, active. In each case *B* shows the effect of the perfusate, tested in a constant ratio to two strengths of acetylcholine—at *A* and *C*, that at *C* being double that at *A*. *a*, effects on the arterial pressure of an eserinized cat under chloralose: *b*, isolated heart of the frog (individual contractions fused in record); *c*, eserinized rectus abdominis muscle of the frog; *d*, eserinized leech muscle. (After Dale and Feldberg[216] from Cannon and Rosenblueth: *Autonomic Neuro-Effector Systems*, New York, 1937, The Macmillan Company.)

frog's heart; intestinal strip from a rabbit; isolated and eserinized frog's rectus abdominis muscle; cat's denervated gastrocnemius. Since the responses of no one of these is specific, several should be tried and various means of distinguishing between their reactions to acetylcholine and other substances should be resorted to. If the action of an extract or perfusate is increased by eserine and is rapidly destroyed by blood or addition of alkali, but not by boiling, there is good reason to believe that acetylcholine is present; no other known substance in the body possesses this combination of properties. The influence of atropine may also be tested. Above all, it is important to quantitate the unknown in terms of acetylcholine (Fig. 66). When this is done the results of all the tests should be the same, if one is to conclude that acetylcholine is present in the extract or perfusate.

The Mediator of Sympathetic Postganglionic Impulses.—It was T. R. Elliott who made (in 1904) the first suggestion that nerve impulses are mediated

by a chemical substance. Having found that adrenalin mimics the action of sympathetic impulses and knowing that section and degeneration of the postganglionic fibers do not interfere with this action, he raised the question whether impulses in sympathetic fibers do not produce their peripheral effects by liberating adrenalin or some closely related substance. It was not until seventeen years later that Elliott's suggestion received the support of actual experimental evidence. In 1921, as has already been mentioned, Loewi not only demonstrated the liberation of "vagus substance," but also showed that when the sympathetic fibers of the frog's heart are stimulated, the solution in contact with it becomes endowed with cardio-acceleratory powers. Next, a long series of classical experiments by Cannon and his collaborators established the general fact that an adrenalin-like substance is given off wherever sympathetic impulses reach an effector. It was shown that the heart, the salivary glands, the nictitating membrane, and other organs, deprived of sympathetic innervation, respond as if activated by sympathetic impulses when sympathetic fibers leading to other

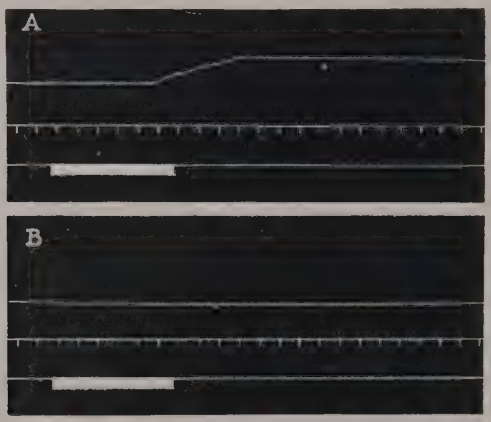

Fig. 67.—Record indicating elaboration of sympathin. *A*, contraction of the nictitating membrane (sensitized by denervation and cocaine) on stimulating the sympathetic nerves (pilomotor) to smooth muscles of the hairs in a patch of skin on the rump of a cat. *B*, absence of the effect when the same stimulus was repeated after removal of the patch of skin. (From Cannon and Rosenblueth: Am. J. Physiol. **99**: 398, 1932.)

effectors are stimulated (Fig. 67). It was demonstrated that such results are entirely dependent on communication through the blood stream. Cannon and Bacq gave the name *sympathin* to the substance produced under the influence of sympathetic postganglionic impulses. Like adrenalin it enters the blood stream and circulates for a short time before it is destroyed or inactivated. Effectors which for some time have been deprived of their sympathetic innervation become extremely sensitive to sympathin and make excellent indicators of its presence in the blood stream. They may also be sensitized by cocaine. The denervated heart and the denervated nictitating membrane of the cat have especially been used for the detection of this substance. Cannon has secured in this way the only direct proof of the elaboration of a mediator in the intact unanesthetized animal: after the central connections of the adrenal glands and of all sympathetic ganglia except one or two in the lower thorax had been severed,

the denervated hearts of cats accelerated during emotional excitement, but this response was permanently abolished when the remaining ganglia were removed. The elaboration of sympathin is readily demonstrable in anesthetized animals; an example is shown in Fig. 67.

In general sympathin has the chemical and physiological properties of adrenalin. Some experiments by Cannon and Rosenblueth indicate that the two are not, however, identical. The results of these experiments have also led them to the conclusion that there are two forms of this mediator: sympathin E, given off from smooth muscle which is excited to contract by sympathetic impulses, and sympathin I, from smooth muscle inhibited by those impulses. The matter remains controversial, Loewi and Bacq, among others, denying that there are two kinds of sympathin and even that there is any difference between sympathin and adrenalin.[34, 85]

The fact that sympathetic denervation renders an effector (gland, smooth muscle or heart muscle) more sensitive to adrenalin and sympathin is of practical and theoretical interest. In the first place it shows conclusively that these substances act independently of the nerves. It is a fact also that the process of sensitization requires a certain amount of time. This has been investigated by Hampel[223] who found that after removal of the superior cervical ganglion the nictitating membrane becomes more and more responsive to a standard intravenous injection of adrenalin up to the end of 14-16 days when a maximum is reached. He also showed that cutting the preganglionic fibers causes an increase of responsiveness, but this is only about half as great as that which follows denervation. This fact is of significance in the surgical treatment of various disorders of sympathetically innervated organs by interruption of the nerve supply. Certain types of vascular spasm (e.g., Raynaud's disease) are at least temporarily relieved by sympathectomy. If the ganglia supplying the affected part are removed the sensitivity to sympathin and adrenalin will eventually become so great that severe attacks may be brought on when the subject becomes emotionally excited, is exposed to cold or suffers hypoglycemia (see Fig. 193, page 475). Whenever possible it is desirable that the sympathectomy be accomplished by interruption of preganglionic fibers.

The Chemical Mediation of Excitation in Sympathetic Ganglia.—This subject has been discussed in Chapter XII and only the main facts need be mentioned here. In his studies of the pharmacological actions of acetylcholine Dale (1914) noted that this substance has, in addition to its muscarine-like action on parasympathetically innervated effectors, an effect on autonomic ganglia which resembles that of nicotine, i.e., it is excitatory in relatively small doses, but becomes paralyzing when its concentration is high. Since 1934 Dale and his co-workers have accumulated evidence which indicates: (1) that acetylcholine is liberated when preganglionic impulses arrive at a sympathetic ganglion, and (2) that perfusion of very small concentrations of acetylcholine through such a ganglion stimulates the postganglionic cells to discharge impulses.[82] Feldberg and Vartiainen made the suggestive discovery that when eserine is perfused through the superior cervical ganglion in very slight concentration (1 in 10^6) the contractions of the smooth muscle of the nictitating membrane which follow submaximal preganglionic stimulation are markedly augmented. This finding appeared to give further support to the hypothesis that acetylcholine is a necessary agent in the transmission of nerve impulses across the synapses of the ganglion.

Cholinergic and Adrenergic Fibers.—So far in this discussion it has been implied (in the interest of clarity) that there is an exact correspondence between the anatomical origin of autonomic fibers and the type of mediator they produce. It is, however, not true that impulses in all postganglionic fibers connected with the thoracolumbar outflow act through liberation of sympathin. There are a number of exceptions to that general rule. The innervation of the sweat glands is indisputably sympathetic from an anatomical point of view, but adrenalin does not produce secretion of sweat, and atropine blocks the response to stimulation of sudomotor nerves (a parasympathetic effect). This anomaly was explained when Dale and Feldberg[217] showed that during sympathetic stimulation a substance having all the properties of acetylcholine appears in the effluent of the vessels of the cat's paw when sweating occurs on the pads (but not when

the vessels from the glands are occluded). There is also evidence showing that vasodilator fibers which act through liberation of acetylcholine course in certain sympathetic trunks. A further complication is set up by the group of facts presented in the preceding paragraph. Acetylcholine is produced in sympathetic ganglia by the arrival of impulses in preganglionic fibers. The latter are assuredly sympathetic. Further, Feldberg, Minz and Tsudzimura[218] have shown that acetylcholine is liberated by impulses reaching the endings of sympathetic preganglionic (splanchnic) fibers in the adrenal medulla, and that this substance is capable of causing a discharge of adrenalin (nicotine-like effect). It is clear that sympathin is not the only mediator of impulses in the sympathetic system.

In 1933 Dale[215] proposed that the words "cholinergic" and "adrenergic" be applied to autonomic fibers "so that we may distinguish between chemical function and anatomical origin." On this basis one can say that postganglionic parasympathetic fibers are mostly, perhaps entirely, cholinergic. There is at present only the merest suggestion that a few may be adrenergic. On the other hand, while postganglionic sympathetic fibers are predominantly adrenergic, there is definite evidence that some are cholinergic. Whether or not acetylcholine is actually the transmitter of excitation in sympathetic ganglia (see Chapter XII), it seems clear that preganglionic sympathetic fibers as a class are cholinergic. It is generally assumed that preganglionic parasympathetic fibers are cholinergic. The inaccessibility of the ganglia of this system makes it difficult to determine what chemical substance may be produced in them. Fig. 68 illustrates only the general rule that postganglionic sympathetic fibers are adrenergic and postganglionic parasympathetic fibers cholinergic. We have already seen that the motor fibers to skeletal muscle may be regarded as cholinergic.

The discovery that nerves can be classified as cholinergic or adrenergic aids in the explanation of certain peculiarities concerning the compatibility of cross-sutured nerves. Langley and Anderson discovered that on regeneration cross-sutured somatic motor fibers can replace autonomic preganglionic fibers, i.e., they establish functional connections at the ganglia, and on stimulation produce effects in the area of distribution of the postganglionic fibers. Similarly, preganglionic fibers can replace other preganglionic fibers. Also, preganglionic fibers of either the parasympathetic or sympathetic systems may be made to innervate skeletal muscle. On the other hand, no one has ever succeeded in obtaining an effective union of motor fibers with postganglionic sympathetic fibers, nor can the latter be replaced by preganglionic fibers of either system. Anderson, in 1905, however, succeeded in obtaining an effective innervation of the sphincter muscle of the iris by preganglionic oculomotor fibers (parasympathetic) after removal of the ciliary ganglion with consequent degeneration of the postganglionic fibers to the muscle. The combination of facts just mentioned shows, as Dale has pointed out, that the compatibility of cross-sutured nerves depends on whether the regenerating nerve is cholinergic or adrenergic. Preganglionic autonomic fibers or motor fibers to a skeletal muscle are interchangeable; all are cholinergic. Postganglionic fibers of the sympathetic can only replace other fibers of the same group; both are adrenergic.

The Significance of the Chemical Mediators in the Functioning of the Autonomic System.—The properties of the mediators are such that they must exert their chief physiological actions locally, close to the site of their elaboration. When one considers the extreme rapidity with which even large amounts of acetylcholine are destroyed by cholinesterase in tissues and blood, it is seen that this substance cannot act as a true hormone. In contrasting the two divisions of the autonomic system, it was pointed out that the adrenal medulla has no counterpart in the parasympathetic system. This provision is of course corre-

lated with the fact that general activity in the parasympathetic does not occur; if it did the results would be physiologically incongruous. It is possible that under normal conditions sympathin may act as a hormone and cooperate with adrenalin. Most of the evidence for the production of sympathin has come from experiments in which the substance was detected in the circulating blood. It must be remembered, however, that its detection has depended on the sensitization of effectors by sympathetic denervation or cocainization or both. There is, accordingly, some doubt whether effectors possessed of a normal innervation are acted on to any significant extent by sympathin produced elsewhere in the body.

The Validity of the Doctrine of Chemical Mediation.—Taken as a whole, the evidence in favor of the view that the effects of impulses in postganglionic autonomic fibers are mediated by chemical transmitters is overwhelming. There are at present available no experimental facts which are seriously opposed to the

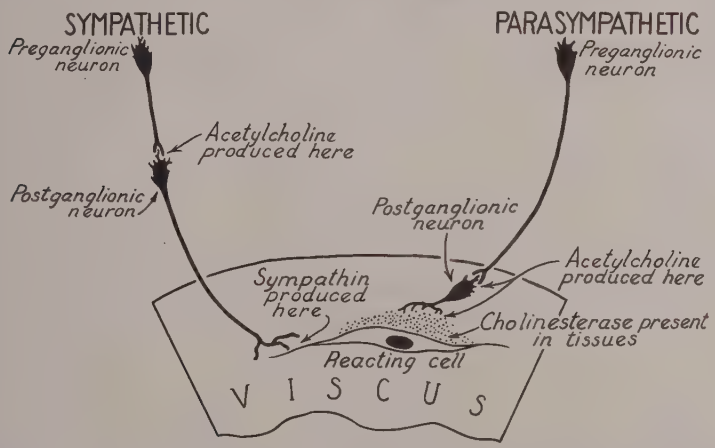

Fig. 68.—Diagram of cholinergic and adrenergic fibers of the autonomic system showing the sites of production of acetylcholine and sympathin. As noted in the text there are certain exceptions to the general rule that postganglionic sympathetic fibers are adrenergic. (Slightly modified from Meyerson: J. A. M. A. **110**: 101, 1938.)

view. To be sure the phenomenon of chemical mediation is inferred and, as Cannon and Rosenblueth remark, "No one has seen the process whereby nerve impulses first produce a chemical substance and the chemical substance then provokes its peculiar effect in the reacting cell." It is also true that no one has directly observed the actual secretion of adrenalin by the cells of the adrenal medulla when the splanchnic nerves are stimulated, but the occurrence of this process stands unchallenged. After all, this much is certain: impulses in postganglionic fibers lead to the elaboration of specific substances in quantities sufficient to produce physiological changes and these effects are qualitatively the same as those produced by nerve stimulation. Much of course remains to be determined. Perhaps the most pressing problem is the explanation of the fact that each mediator exerts excitatory effects in some organs and inhibitory effects in others.

THE CENTRAL MECHANISMS CONTROLLING THE AUTONOMIC NERVOUS SYSTEM

The normal discharge of nerve impulses to visceral effectors is entirely dependent on the central connections of the outlying autonomic neurons. Since the cell bodies of all preganglionic neurons lie within the brain stem or spinal cord, it is obvious that these elements form the primary central representation of the autonomic system. Thus the nucleus of Edinger-Westphal is the primary motor center of the parasympathetic innervation of the sphincter of the pupil. Similarly, the salivatory nuclei and the various visceral motor components of the vagal nuclei represent the immediate sources of parasympathetic impulses destined for salivary glands, bronchioles, myocardium, coronary vessels, and that part of the gastrointestinal tract lying above the ileocolic junction. Gaskell and others have shown that the cell bodies of the sympathetic preganglionic neurons lie in the lateral horns of the spinal cord. Indeed, the intermediolateral columns of gray matter which form the lateral horns are restricted to those portions of the cord from which the gray rami arise. The fibers which constitute the sacral part of the parasympathetic outflow originate from cells in the lateral column of gray matter in the sacral segments of the cord.

To these visceral efferent neurons we may apply the concept of the final common path, but we cannot at present discern with any anatomical exactness the central channels over which impulses of diverse origins act on them. The evidence which is at hand comes very largely from physiological studies and for the most part has to do with the sources of remote control rather than with the paths through which that control is exerted. Consideration of the general functions and conditions of activity of the autonomic system indicates that its central representation must be of such character as to account for the following facts: tonic discharge in a large fraction of the preganglionic fibers; the exertion of excitatory and inhibitory influences on the final common path, often in such manner as to assure reciprocal innervation; the capacity of certain individual components of the system, especially in the cranial and sacral portions, to act independently; the tendency of the sympathetic division to go into action as a unit; and, finally, the cooperation of visceral effectors in the activities of the cerebrospinal system.

Spinal and Bulbospinal Autonomic Mechanisms.—All the available evidence favors the view that the various tonic and reflex discharges which regulate cardiovascular activities are managed by central mechanisms situated below the mesencephalon.[204, 236] It was long ago established that the normal tonic vasoconstrictor discharge continues and pressor and depressor vascular reflexes remain unimpaired after transection of the brain stem at an upper pontile level (Owsjannikow, 1870; Dittmar, 1873). Not so much is known about other autonomic functions. A center for the reflex mobilization of blood sugar through sympathetic discharge to the adrenal medulla has been located in the lower pontile region by Brooks.[205] There is evidence that the reflex control of the urinary bladder through the sacral autonomic outflow is chiefly spinal and bulbospinal (see Chapter LXXXIII).

The method of localized electrical stimulation has revealed pressor and depressor regions on the floor of the fourth ventricle (Ranson and Billingsley[231]). Recently Wang and Ranson[232] explored the pontile and bulbar areas in depth by means of small stimulating electrodes which could be placed with precision

in any desired locus by means of the Horsley-Clarke instrument. They found that throughout the pons and upper medulla relatively mild pressor responses can be obtained from the lateral reticular formation and the adjacent periventricular area. The effects are due to stimulation of fibers from the hypothalamus which descend in these portions of the rhombencephalon. Much more marked rises in arterial pressure were evoked on excitation of the caudal half of the floor of the fourth ventricle and the underlying lateral reticular formation. Since the greater magnitude of these effects cannot be explained adequately on the basis of a possible concentration of descending fibers, the results suggest that they signal the stimulation of cells and fibers belonging to the bulbar sympathetic pressor center whose existence at this level is indicated by transection experiments. This interpretation was further supported by evidence which showed that the results could not be due to reflex stimulation of an ascending afferent tract to suprabulbar levels; the lower bulbar region remains active after decerebration (Wang and Ranson[233]). Depressor responses were obtained from various pontile and bulbar regions, but the points yielding the greatest drops in arterial pressure (with the vagi cut) appeared to be concentrated near the rostral end of the nucleus gracilis and the adjacent portion of the area postrema. This region therefore probably contains an important part of the bulbar depressor apparatus.

Immediately after a cervical transection of the spinal cord, the arterial pressure drops to a low level and no vasomotor reflexes can be elicited. This is one aspect of spinal shock (see page 83). With the discovery of reflex activity in skeletal muscles, the pressure rises and attains its normal level when large pressor responses can be obtained by nociceptive stimulation. That even the low level of pressure during spinal shock is partly due to a residuum of spinal vasotonic influence is shown by the further reduction in pressure which then results from splanchnic section or destruction of the cord. When recovery from spinal shock has occurred, many sympathetic reflexes can be elicited.[206] Under normal conditions, however, it is probable that the cord acts merely as a pathway for these reflexes, which are essentially bulbar; at least the normal pressor reflex arc is not complete within the cord (Ranson[229]). Much of the activity of the sacral autonomic system also depends on supraspinal levels. For example, the permanent disorders of micturition shown by spinal animals and spinal man indicate that the cord does not suffice for the proper carrying out of this act (see Chapter LXXXIII). It is normally dependent upon the integration of a number of reflexes, at least two of which are managed by mechanisms situated at bulbar or mesencephalic levels. The cerebral cortical (voluntary) control is apparently exerted through these reflex mechanisms.

Suprabulbar Autonomic Mechanisms.—Application of the method of localized electrical stimulation has revealed two regions in the cerebrum especially concerned in the discharging of impulses which produce activity in the autonomic neurons. These are the hypothalamus and the cerebral cortex. In addition, experiments involving ablation and localized destruction of cerebral tissue have also shown that these two regions exert pronounced effects on the various autonomic outflows of brain stem and cord.[124, 203, 230] *The hypothalamic representation of the autonomic will be discussed in the next chapter.* A brief account of the relationship of cortical mechanisms to autonomic functions may be given here.

Autonomic responses have frequently been elicited by stimulation of various regions of the cerebral cortex. The most pronounced effects are obtained from the motor and premotor areas and consist of changes in arterial pressure, pupillodilatation and inhibition of gastric peristalsis (see Fulton;[124] Hoff and Green;[225] Green and Hoff[222]). Vasomotor, pilomotor, sudomotor and certain gastrointestinal disturbances have been found after cortical ablations.[124] The significance of such results remains problematical, but it is reasonable to suppose that the autonomic representation in the cortex is concerned with the visceral concomitants of activity in skeletal muscle induced by neural discharges of cortical origin. It is also likely that this representation is a part of the central temperature-regulating mechanism, for removal of the cerebral cortex in dogs and cats disturbs certain reactions to cold and heat (Pinkston, Bard and Rioch[255]). This whole subject is one which demands further study.

CHAPTER XVII

THE HYPOTHALAMUS

Twenty years ago the hypothalamus was a neglected and physiologically obscure part of the brain. It received little if any mention in textbooks of physiology, and the majority of anatomical treatises merely classified it as the most ventral part of the diencephalon, pointed out its embryological relationship to the pituitary gland and pronounced it, on the basis of comparative studies, an important olfacto-visceral correlation center. In 1940 a symposium on the anatomy, physiology, and clinical significance of the hypothalamus included forty-two investigators and the published Proceedings* contains thirty-four chapters, runs to 971 pages and includes a bibliography of more than one thousand titles. A mere examination of these references suggests that this part of the brain exerts an influence either directly or indirectly upon almost every aspect of the bodily economy. But when one scrutinizes the actual evidence it is plain that the established functions of the hypothalamus can be discussed under a few headings. Before proceeding with such a discussion a brief anatomical account of the hypothalamic region is essential.

MORPHOLOGICAL FEATURES OF THE HYPOTHALAMUS

Major Anatomical Relationships

The hypothalamus is an ancient part of the forebrain (prosencephalon) which, unlike the cerebellum and the cerebral hemispheres, has maintained throughout its phylogenetic history a relative constancy of arrangement. It is relatively larger in the lower vertebrates than in the higher, but according to Clark[241] this difference is due more to the small size of the forebrain as a whole in these forms than to any greater intrinsic importance of the hypothalamus in the more primitive animals. In all vertebrates it makes up the floor of the third ventricle. The cellular elements of the hypothalamus belong to the diencephalic portion of a column of gray matter which on each side extends from the preoptic area into the tegmentum of the mesencephalon (midbrain).

The Medial Forebrain Bundle.—Intimately associated with the hypothalamic neurons is the medial forebrain bundle which arises in the ventromedial centers of the cerebral hemisphere (olfactory bulb and peduncle, the anterior perforated substance, septum, the parolfactory region, the amygdaloid nucleus and the anterior part of the hippocampal formation). The fibers of this tract run into and through the lateral parts of the preoptic region and the hypothalamus (Fig. 69). Many terminate in the hypothalamic nuclei while others, joined by fibers of hypothalamic origin, pass diffusely into the mesencephalic tegmentum.

**The Hypothalamus, Vol. 20, Research Publications of the Association for Research in Nervous and Mental Disease*, Baltimore, 1940, Williams and Wilkins. This volume is the most exhaustive account of the hypothalamus that is available. The student is, however, especially referred to the excellent and understandable presentation of the anatomy of the hypothalamus by Le Gros Clark in the book by Clark, Beattie, Riddoch and Dott,[241] and to the recent admirable review of hypothalamic functions by Ranson and Magoun.[287]

The medial forebrain bundle is less extensive in the higher mammals than in the lower vertebrates, and this fact is probably a reflection of a phylogenetic shift in the general physiological status of the hypothalamus from an organ which is predominantly an olfactory correlation center to one which serves as an integrating mechanism for several quite distinct patterns of behavior having no relation to the sense of smell. Nevertheless, what appears to be the caudal extension of this bundle constitutes in the mammals a diffuse efferent projection system of hypothalamic fibers which is of considerable physiological importance.

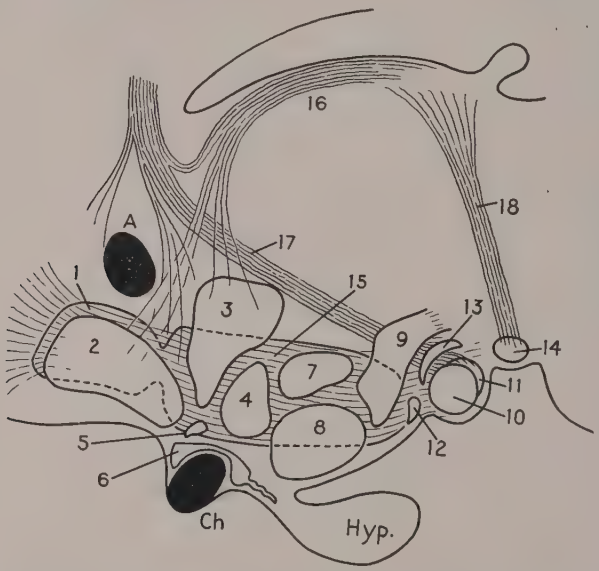

Fig. 69.—Diagram showing the relative positions in a sagittal plane of the hypothalamic nuclei in a typical mammalian brain and their relation to the fornix (17), stria habenularis (16) and fasciculus retroflexus or habenulo-peduncular tract (18). *A*, anterior commissure; *Ch.*, optic chiasma; *Hyp.*, hypophysis; *1*, lateral preoptic nucleus (permeated by the medial forebrain bundle); *2*, medial preoptic nucleus; *3*, paraventricular nucleus; *4*, anterior hypothalamic area; *5*, suprachiasmatic nucleus; *6*, supraoptic nucleus; *7*, dorsomedial hypothalamic nucleus; *8*, ventromedial hypothalamic nucleus; *9*, posterior hypothalamic nucleus; *10*, medial mammillary nucleus; *11*, lateral mammillary nucleus; *12*, premammillary nucleus; *13*, supramammillary nucleus; *14*, interpeduncular nucleus (a mesencephalic element in which the habenulo-peduncular tract terminates); *15*, lateral hypothalamic nucleus (permeated by the medial forebrain bundle). (From Le Gros Clark: *The Hypothalamus*, Edinburgh, 1938, Oliver and Boyd.)

The Hypothalamico-Hypophysial Relationship.—A second anatomical relationship which is a constant feature of the hypothalamus is its intimate association with the hypophysis or pituitary gland. The neural portion of this gland (the neurohypophysis) is an embryological derivative of the floor of the third ventricle, and there are physiological as well as anatomical reasons for regarding the relationship between hypothalamus and neurohypophysis as similar to that which exists between the lateral horns of the spinal cord and the adrenal medulla. In both cases connecting nerve fibers act upon cells which, though of neural origin, have secretory functions.

An understanding of the hypothalamico-hypophysial relationship requires a clear idea of the anatomical subdivisions of the pituitary gland. This in turn depends upon the cor-

rect use of the various terms which are applied to these subdivisions. The most logical system of nomenclature is the one adopted by Rioch and Wislocki[260] who have presented the major divisions and subdivisions of the mammalian hypophysis as follows:

Major divisions and subdivisions of the mammalian hypophysis

	Major Divisions	*Subdivisions*	
Adenohypophysis	Lobus Glandularis	1. Pars distalis *(Anterior lobe)* 2. Pars tuberalis 3. Pars intermedia	
Neurohypophysis	Lobus Nervosus (Neural lobe)	1. Infundibular process	*Posterior lobe*
	Infundibulum (Neural stalk)	1. Infundibular stem 2. Median eminence of tuber cinereum	*Neural stalk,* together with sheath of portions of lobus glandularis, designated as *hypophysial stalk*

The neurohypophysis is distinguished from the glandular lobe or adenohypophysis which is of buccal derivation. It consists of the median eminence of the tuber cinereum, the infundibular stem, and the neural lobe (see Fig. 355). The three parts have the same histological structure. The median eminence and the infundibular stem together with an investing sheath of pars tuberalis, belonging to the adenohypophysis, make up the hypophysial or pituitary stalk. The terms infundibulum and pituitary stalk should be used synonymously. The hypophysis includes more than is indicated by the usual division of the gland into anterior and posterior lobes. In mammals the residual lumen of the gland forms a natural line of cleavage between these two parts and after removal from the sella turcica, with breaking of the stalk, it can be readily split into two portions, one consisting of the pars distalis (anterior lobe) and the other of pars intermedia and neural lobe (together the posterior lobe).

It is now generally agreed that fibers of hypothalamic origin enter the hypophysial stalk. According to Rasmussen[258] the number of these fibers is about 10,000 in the rat, 60,000 in the dog and monkey, and 100,000 in man. Their physiological significance will be discussed in the section devoted to the functions of the hypothalamus.

The Subdivisions of the Hypothalamus

For descriptive purposes the mammalian hypothalamus may be subdivided rostro-caudally into three regions (Le Gros Clark[241]): (1) a rostal or supraoptic region which lies above the optic chiasm; (2) the region of the tuber cinereum to which is attached the stalk of the hypophysis; and (3) a caudal or mammillary region. Within these parts are groups of cells of which some are so diffuse that they can be distinguished only by their general relationship to more definite structures while others form distinct nuclei. For the former the term area is more suitable than nucleus. The major divisions, nuclei and areas of the hypothalamus have been listed in similar fashion by Clark[241] and by Rioch and Wislocki.[260] The following outline constructed from their tables will serve, together with Fig. 69, to convey some idea of the arrangement of gray matter in the hypothalamus.

I. Supraoptic or Rostral Region
- a. Supraoptic nucleus (6)*
- b. Paraventricular nucleus (3)
- c. Suprachiasmatic nucleus (5)
- d. Anterior hypothalamic area (4)
- e. Lateral hypothalamic area (15)

*The numbers in parentheses correspond to those which designate the nuclei shown in Fig. 69.

II. Tuberal or Infundibular Region
- a. Dorsomedial hypothalamic nucleus (7)
- b. Ventromedial hypothalamic nucleus (8)
- c. Posterior hypothalamic area (9)
- d. Arcuate nucleus
- e. Lateral hypothalamic area (15)

III. Mammillary or Caudal Region
- a. Medial mammillary nucleus (10)
- b. Nucleus intercalatus
- c. Lateral mammillary nucleus (11)
- d. Premammillary area (12)
- e. Supramammillary area (13)
- f. Lateral hypothalamic area (15)

Although not a part of the hypothalamus proper, the *preoptic areas,* belonging to the telencephalon, are usually described with the hypothalamus. They represent the rostral extension of the column of gray matter which forms the nuclear portions of the hypothalamus. The preoptic region lies above and ahead of the optic recess and extends dorsally as high as the anterior commissure (Fig. 69). It is divided into two parts: the medial preoptic area lying close to the ependymal lining of the third ventricle and the lateral preoptic area which is a direct rostral prolongation of the lateral hypothalamic area and like it is permeated by the medial forebrain bundle.

The details of the anatomical and cytological features of the hypothalamus cannot be entered into here. But a few facts which are of significance in the light of our present physiological knowledge of this region will be mentioned. It should be noted that the lateral hypothalamic area is common to all three subdivisions. It is continuous rostrally with the lateral preoptic area and caudally with the tegmental gray matter of the mesencephalon. This part of the hypothalamus lies lateral to the nuclei which border the third ventricle and medial to the optic tract, subthalamus, and cerebral peduncles. It consists of cells of moderate size scattered among the fibers of the medial forebrain bundle. The most sharply circumscribed cell group of the hypothalamus is the nucleus supraopticus which overlies the lateral part of the chiasm and the beginning of the optic tract. Its cells, which are large and densely packed, have a more intimate relation to capillaries than any other nerve cells. Indeed the supraoptic nucleus has the richest capillary bed found in the central nervous system —2,600 capillaries per cubic millimeter of tissue.[243] Its nearest competitor in this respect is the nearby paraventricular nucleus which contains only about one-half as many capillaries per unit of cells; outside the hypothalamus capillary counts tend to fall well below 1,000.

The Connections of the Hypothalamus

Physiological evidence shows that many sensory stimuli are capable of influencing neural mechanisms in the hypothalamus and that the hypothalamus discharges impulses which cause or modify reactions in a large part of the visceral and skeletal effectors of the body. These facts make it plain that the hypothalamus must have abundant connections, both afferent and efferent, with other parts of the central nervous system. But the connections which have been traced by anatomical methods are for the most part poorly defined. With the exception of the mammillothalamic tract (bundle of Vicq d'Azyr)

and the fornix, which are compact bundles of well-myelinated fibers, the hypothalamic projections are diffuse and made up of small myelinated and unmyelinated fibers. Even the extremely important hypothalamico-hypophysial fibers, whose collection in the narrow funnel of the pituitary stalk might be expected to facilitate their study, are differentiated with such difficulty that their very existence was questioned or denied by anatomists until the force of physiological evidence recently led to a renewal of efforts to demonstrate them. A number of afferent and efferent paths are known, but the origins of the former and the terminations of the latter are in many cases doubtful.

Afferent Connections.—One of the most definite of these is the *medial forebrain bundle,* already described. It brings the hypothalamus under the influence of the basal olfactory regions of the hemisphere and the hippocampus. It may be doubted that in the higher forms this influence is entirely olfactory. The *periventricular system* of fibers probably serves to convey impulses into the hypothalamus. This group of extremely fine fibers courses vertically close to the third ventricle and some of its elements appear to connect the midline thalamic nuclei with hypothalamic nuclei, especially the more caudally situated ones. The *fornix* connects the hippocampal cortex with the hypothalamus; most of its fibers end in the mammillary nuclei, but a few pass to the tuberal region and probably also to the supraoptic region (Fig. 69).

Certain physiological evidence suggests that the hypothalamus must be under the influence of the cerebral neocortex, but no direct pathway is known. *Indirect corticohypothalamic connections* may be made by relays through either the thalamus or the basal olfactory centers. Physiological facts also suggest that there are ascending sensory pathways to the hypothalamus. Impulses from the spinal cord and brain stem may reach the hypothalamus through the thalamus, but the fact that vigorous reactions which depend on the integrity of the hypothalamus occur after practically all the thalamus has been cut away (Bard[203]) suggests a more direct connection. This, according to Clark,[241] may be the *mammillary peduncle,* a small and poorly defined tract which detaches itself from the medial lemniscus, passes forward on either side of the interpeduncular nucleus and terminates in the lateral part of the mammillary complex and possibly also more rostrally in the hypothalamus.

Efferent Connections.—The efferent paths from the hypothalamus fall into three main groups (Ranson and Magoun[257]). These are (1) to the thalamus with probable relays to the cortex, (2) to the brain stem and spinal cord, and (3) to the hypophysis.

The chief path to the thalamus is the *mammillothalamic tract* (bundle of Vicq d'Azyr) connecting the medial mammillary nucleus with the anterior thalamic nuclei which relay to the gyrus cinguli of the neocortex. Other hypothalamothalamic connections are probably made through the *periventricular system,* but this system is more conspicuous as an efferent projection to the mesencephalic and bulbar regions. Its fibers arise from the dorsomedial, ventromedial, and posterior hypothalamic nuclei, curve upwards and backwards, pass just under the posterior commissure and form a longitudinal bundle (the fasciculus longitudinalis dorsalis of Schütz) which runs just ventral to the aqueduct for some distance caudally. Physiological evidence indicates that this group of fibers is a less important descending projection than *fibers which run from the lateral hypothalamic area dorsolateral to the mammillary bodies*

into the reticular formation of the mesencephalon and which by relays convey impulses caudally to the bulbar and spinal motor nuclei (Magoun, Ranson and Hetherington;[254] Magoun[253]).

The *hypothalamico-hypophysial* tract brings the pituitary gland under the control of the hypothalamus. According to Ranson and his associates[244, 257] it consists of two parts. The first and better known is the supraopticohypophysial tract which arises from the supraoptic nuclei and possibly also from the paraventricular and other anterior nuclei of the hypothalamus, loops over the chiasm and, after coursing medially along the base of the anterior hypothalamus, enters the median eminence, infundibular stem, and neural lobe. The second is the tuberohypophysial tract which comes from regions close to, but caudal and lateral to, the infundibulum and occupies the dorsal wall of the pituitary stalk. The fibers of both tracts are unmyelinated. The majority terminate in the neurohypophysis, but a few enter the pars intermedia (Fisher, Ingram and Ranson[244]) and even the pars distalis or anterior lobe (Brooks;[237] Brooks and Gersh[239]). There is physiological and cytological evidence that some supraopticohypophysial fibers end in the median eminence and infundibular stem as well as in the neural lobe. Fisher, Ingram and Ranson[244] showed that bilateral interruption of this tract causes atrophy and hypercellularity of these three parts and nearly complete retrograde degeneration of the supraoptic nuclei. Rasmussen[258] has found that after complete removal of the neural lobe 80 to 90 per cent of the supraoptic cells disappear while after lesions which also involve the median eminence practically all the cells disappear. The paraventricular nucleus is much less affected by removal of the neural lobe and infundibular stem, but shows a great loss of cells when lesions involve the median eminence. Such facts indicate the distribution of these fibers of anterior hypothalamic origin.

THE FUNCTIONS OF THE HYPOTHALAMUS

Autonomic Representation in the Hypothalamus

Sympathetic Discharges Evoked by Hypothalamic Stimulation.—It was first demonstrated by Karplus and Kreidl (1909-1927) that many portions of the sympathetic outflow can be made to discharge by electrical stimulation of the hypothalamus. This fact has been confirmed repeatedly by many investigators. Ranson and his collaborators[247, 248, 256] (see summary by Ranson and Magoun[257]) have explored the hypothalamus and adjacent parts of the brain stem in great detail by means of very small stimulating electrodes, which can be inserted to any desired point in the interior of the brain (Horsley-Clarke technique). From this type of investigation it has been made clear that very localized hypothalamic stimulation can produce almost every effect which peripheral sympathetic fibers mediate. Rises of blood pressure from vasoconstriction, dilatation of the pupils and contraction of the nictitating membranes, erection of hair, sweating and medulliadrenal secretion have been obtained. In the anesthetized animal the sympathetic response is usually limited to a rise in arterial pressure, pupillodilatation and retraction of the membranes, but it is accompanied by contraction of the urinary bladder (a parasympathetic effect) and acceleration and increased amplitude of respiration. If the stimulation is continued, and especially if the anesthesia is not deep, running movements and even struggling may occur. The autonomic effects are not second-

ary to the activity in skeletal muscle, for they precede them and are not impaired by doses of curare which completely abolish all somatic activity including respiratory movements. In unanesthetized or lightly anesthetized animals the sympathetic responses are more marked and include inhibition of gastrointestinal activity.[247]

The sympathetic reactions can be elicited by stimulation of any one of many points in the hypothalamus. The active points are distributed throughout the length of the hypothalamus but, except at the levels of the supraoptic and supramammillary decussations, the lateral part is much more responsive to stimulation than the medial.[257] Medial structures such as the ventromedial and dorsomedial nuclei contain very few reactive points. The lateral hypothalamic area is unquestionably the region from which sympathetic discharges can be obtained most readily. The effect cannot be attributed to excitation of fibers of the medial forebrain bundle originating rostral to the hypothalamus, for stimulation of the preoptic area through which most of these fibers pass does not produce sympathetic reactions. Ranson and Magoun[257] point out that since the thalamus, the fornix, and the striatal complex do not yield them and only a few scattered active points can be found in the internal capsule, the sympathetic effects of hypothalamic stimulation are not due to stimulation of pathways which descend through or close to the hypothalamus. Although some sympathetic effects can be elicited by cortical stimulation, there is no evidence that these are mediated through tracts which enter the hypothalamus; indeed general sympathetic effects can be evoked from posterior hypothalamic stimulation in cats after degeneration of all descending fibers of cortical origin (Rioch and Brenner[308]). It may safely be concluded that *the sympathetic discharges obtained from the hypothalamus by punctate stimulation are to be attributed to activation of its own intrinsic mechanism.*

The Hypothalamus and the Parasympathetic System.—It has been claimed, especially by Beattie and by Cushing, that the parasympathetic system has a definite representation in the hypothalamus. Beattie advanced the theory that the hypothalamus is divisible into an anteriorly situated "parasympathetic center" and a posteriorly placed "sympathetic center." But this idea was based on relatively crude methods and has not been substantiated by subsequent findings. Ranson and his collaborators[230, 257] have obtained results which indicate that the parasympathetic discharges which are obtainable by hypothalamic stimulation are due to excitation of fibers which descend through the lateral hypothalamic area from more rostral regions. They evoked one definite parasympathetic effect, namely, contraction of the urinary bladder, from stimulation of the region of the septum, anterior commissure and the medial preoptic area, and traced the active points caudally in the lateral hypothalamic area and into the upper mesencephalon. Since the contractions may still be elicited in the cat after degeneration of all connections from the frontal poles of the cerebral cortex[252] or after complete decortication,[308] it seems well established that a parasympathetic center for the bladder is situated just rostral to the hypothalamus. Whether this region exerts any other parasympathetic effects is not clear. Falls in blood pressure and peripheral vasodilation which have been obtained from it may be due to inhibition of sympathetic activity. It is possible that increased gastrointestinal activity due to augmented vagal discharge can be produced from this general region, especially when the stimulation is so weak that it does not involve hypothalamic activation of the opposed sympathetic innervation of the gut.

Cushing[242] proposed the theory that parasympathetic activity is provoked from the hypothalamus by an active principle of the posterior lobe of the pituitary gland. His evidence came from the remarkable effects obtained by injections of pituitrin into the lateral ventricle of the human brain. When the hypothalamus of the patient was intact, vaso-

dilation, sweating, lowering of the basal metabolic rate, salivation and signs of increased vagal activity of the stomach followed the injection. On the other hand, when the hypothalamus was flattened by hydrocephalus or destroyed by a tumor, these reactions could not be obtained. Only two of them, salivation and the gastric effects, can be definitely attributed to increased parasympathetic activity; the abolition of all of them by atropine did not actually constitute proof to the contrary. Much less definite results were obtained when the experiments were repeated on animals. Since, as we have seen, the existence of a hypothalamic parasympathetic center or mechanism cannot be established by more direct methods, Cushing's interpretation must be rejected. Rioch[259] has suggested that the results reported "were due to nonspecific (possibly vasoconstrictor) effects at the region of the floor of the fourth ventricle, affecting chiefly the vagal and depressor mechanisms."

Gastrointestinal Hemorrhage and Erosions.—Many experimental workers and not a few clinical observers have noted the occurrence of erosions of the gastric and intestinal mucosa following intracranial operations or in association with intracranial tumors which involve the hypothalamic region. A great diversity of opinion and results characterizes the literature of this subject. In a recent critical review Sheehan[261] concludes that experimental injuries of the hypothalamus are followed by gastrointestinal changes much more frequently than are lesions placed anywhere else in the central nervous system. To obtain mucosal hemorrhage and erosion the hypothalamic injury must be large. The most effective site is the tuberal region; lesions in the supraoptic region are less effective and destruction of the mammillary area apparently never leads to the disturbances. The significance of these facts is not clear. One view is that the mucosal changes are due to spasm of terminal vessels resulting from release or irritation of a central sympathetic vasoconstrictor mechanism. But if this effect depends on over-activity of the caudal hypothalamus, it is curious that the development of the gastrointestinal lesions is not accompanied by signs of general sympathetic activity. It is perhaps significant that most of the extra-hypothalamic central lesions which have been associated with these particular peripheral lesions involve descending pathways affecting the autonomic system. The relationship of this group of observations to the etiology of gastric and duodenal ulcer is not at all clear.

The Significance of the Hypothalamic Representation of the Sympathetic System.—Although the results of hypothalamic stimulation in anesthetized animals demonstrate that the sympathetic system has a notable representation in this part of the brain, they actually give no information whatever about the functional significance of this fact. There is no reason to suppose that the hypothalamus is a center essential to the various sympathetic reflexes and tonic discharges (vasomotor and cardiac); these are managed by bulbospinal mechanisms (see page 184). Without doubt the most marked and most general sympathetic discharges occur under conditions which Cannon has designated as emergency states. These include states of strong emotion such as fear and anger, exposure to cold, anoxemia and hypoglycemia. Furthermore, as we have seen, the animal deprived of its sympathetic system suffers marked impairment of function when subjected to any one of these conditions, although it can live quite normally under less stressful circumstances. It is reasonable to ask whether the sympathetic discharges characteristic of emergency states have their origin in the hypothalamus. Actual experimental evidence, which will be mentioned in the next two sections of this chapter, indicates that such is the case in two of these conditions, namely, *exposure to cold* and *strong emotional excitement*. This suggests that *the hypothalamic representation of the sympathetic is merely a part of the neural mechanisms which elaborate the patterned modes of behavior seen in strong emotional excitement and during exposure to cold. Furthermore, since these patterned responses are made up of the integrated actions of somatic and visceral effectors, it is a mistake to regard the hypothalamus as an exclusively autonomic center.*

Temperature Regulation

The general subject of bodily temperature regulation and the role played by the central and peripheral nervous systems in the thermal reactions of the organism are discussed in Chapter LIX. Here it is only necessary to indicate that the hypothalamus is the part of the central nervous system most requisite for the control of body temperature. After lesions which destroy much of the hypothalamus or interrupt at the mammillary level the major descending pathways from this region, mammals become poikilothermic (cold-blooded); the body temperature no longer remains nearly constant in the face of wide variations in environmental temperature, but follows closely the thermal changes of the surroundings. Although other parts of the brain contribute to the process of temperature regulation, none exerts as marked an effect. Cats and dogs in which there has been removed all cerebral cortex, or indeed practically all cerebral tissue above the hypothalamus, show only moderate disturbances in their thermal responses and are quite comparable to their normal fellows in withstanding extremes of environmental cold and warmth.[255] Obviously this part of the brain contains the chief temperature-regulating mechanism.

After destruction of the caudal hypothalamus, exposure to cold does not induce the bodily changes which prevent a fall in temperature. These include muscle tensing and shivering, which are effected through cerebrospinal nerves, and such signs of sympathetic activity as peripheral vasoconstriction, piloerection and medulliadrenal secretion. Also, exposure to external warmth fails to evoke the reactions which permit the necessary loss of heat—peripheral vasodilatation, sweating and, in certain animals a special thermolytic process, the occurrence of panting associated with salivation. Obviously the hypothalamus is here essentially involved in the fashioning of two quite dissimilar patterned responses. Both include changes in skeletal muscle (shivering, panting) as well as alterations due to excitation or inhibition of autonomic discharges. This fact shows that the hypothalamus as a central integrating organ is much more than a mere autonomic center.

There is very good evidence, as we shall see in Chapter LIX, that within the hypothalamus the neural mechanism which acts to prevent overheating has a locus apart from the one which guards against chilling. The former is situated in the region above and in front of the optic chiasm, the latter chiefly in the more caudal portions of the hypothalamus. An anterior lesion may destroy the capacity to withstand heat without impairing the reactions to cold, while extensive damage in the mammillary area causes failure to regulate against both heat and cold. Since lesions placed medially in the hypothalamus behind the chiasm do not interfere with the responses to high temperatures, the descending pathways from the rostrally situated mechanism for heat loss must run in the lateral hypothalamic area and be subject to interruption by injuries which destroy the more caudally placed mechanism for protection against cooling (see Ranson and Magoun[257]).

It is clear that the autonomic responses to cold which depend on the hypothalamus are brought about by sympathetic discharges. These are the ones which are prevented by sympathectomy. There has been an unfortunate tendency, engendered probably by a desire to draw contrasting pictures, to regard the visceral changes evoked by heat as parasympathetic in origin and accordingly to attribute parasympathetic functions to the anterior hypothalamus. But a moment's consideration should convince the reader that none of the autonomically conditioned reactions to environmental heat, except the salivation which

accompanies panting, is definitely of parasympathetic origin. Since there is no known parasympathetic supply to the cutaneous blood vessels, it is reasonable to attribute the cutaneous vasodilatation to inhibition of the normal tonic sympathetic discharge. The participation of dorsal root fibers in this reaction is possible, but they cannot logically be called parasympathetic, as was pointed out in Chapter XVI. Although the innervation of the sweat glands is cholinergic, it is also definitely sympathetic. The one parasympathetic effect, salivation, may be secondary to the panting.

The Hypothalamus and Emotional Expression

Studies of animals, such as cats and dogs, which have long survived removal of the cerebral cortex, show conclusively that the capacity to *display* anger or rage depends on central mechanisms which lie below the cortex. In 1928 Bard[203] showed that the hypothalamus is necessary for the vigorous expression of rage which occurs in freshly decorticate cats either spontaneously or in response to relatively mild stimuli. This "sham rage," as it was called to indicate that in the decorticate animal one is dealing only with the *expression* of anger, is unmistakably the counterpart of the activity which characterizes intense fury in the normal animal. It consists of spitting, a snarling expression, biting, struggling, clawing movements and lashing of the tail, together with all the signs of widespread sympathetic activity (erection of hair, rise in blood pressure, cardiac acceleration, sweating, and the ocular effects of cervical sympathetic discharge). Since the full response appeared after removal of all cerebral tissue above the tuberal region while only individual items of the response could be evoked after transection of the brain behind the mammillary bodies, it was concluded that this expression of anger in the cat is dependent upon central mechanisms which are located in the caudal hypothalamus.

Further evidence that the hypothalamus is concerned in the elaboration and execution of the complex reaction pattern characteristic of anger has been secured by Ranson and his associates.[230, 247, 257] In their experiments the hypothalamus was stimulated in unanesthetized cats through electrodes which had been placed under ether. Stimulation within the hypothalamus and especially in the lateral hypothalamic area produced a reaction quite similar to the sham rage described above. Ranson points out that "the cats behaved as they would have had they been threatened by a barking dog." The response was specifically hypothalamic; it was not obtainable from the thalamus, internal capsule, septum or infundibular stalk unless currents were used which were of such strength that they spread to the hypothalamus. These observations are in full agreement with the conclusions previously reached on the basis of the study of decorticate sham rage. Together the two lines of investigation show quite clearly that the *hypothalamus contains a mechanism whose activation produces the reaction pattern characteristic of rage.* Nevertheless there are reasons for believing that typical expressions of anger can be produced by other parts of the central nervous system although probably not with the full violence characteristic of the hypothalamic response. Keller[250] has obtained rage responses in cats which he succeeded in maintaining for as long as eighteen and twenty days after mesencephalic transection of the brain stem (decerebration) and just recently Magoun and Bard have convinced themselves that very pronounced displays of feline anger can be evoked in cats in which the entire caudal third of the hypothalamus had been destroyed but whose brains were

otherwise intact. It is not easy to appraise the true meaning of such results. In any event there can be no doubt that the hypothalamus is organized in such a way as to shape or facilitate the somato-visceral reaction pattern which we call an expression of rage. It may be pointed out here that evidence from the clinic suggests that the human hypothalamus plays a role in shaping the emotional actions and feelings of man (Alpers).

The excessiveness and easy elicitation of the decorticate sham rage seen in acute experiments suggest that the hypothalamic mechanism is in a state of overactivity or hyperexcitability. The behavior might therefore be regarded as a release phenomenon denoting the removal of inhibition. Since the pattern and threshold of the sham rage were found to be the same after ablation of neocortex without damage to subcortical structures as after decortication plus transection of the brain stem just above the caudal hypothalamus, it was suspected that the cortex is the source of an inhibitory effect holding the hypothalamus in check. The possible pathways by which such an influence might be exerted have been discussed above. A study of a number of chronically decorticate cats and dogs has shown that the reactions of these animals to a given rage stimulus (a pinch) are sometimes greater, sometimes less, than before the operation.[234, 269] The cortex therefore probably normally exerts both inhibitory and excitatory effects either directly on the hypothalamus or upon final paths which it has in common with the hypothalamus. In putting emphasis on the hypothalamus as a source of emotional behavior it must not be forgotten that the cerebral cortex, whatever its functional relationship to the hypothalamus may be, enormously increases the number of circumstances which are capable of acting as emotional stimuli. This it does through the well-known process of conditioning or learning (see Chapter XX) and by adding discrimination to simple sensory processes. A decorticate dog, for example, never shows anger in response to any particular visual or auditory stimulus; on the other hand, everyone knows that a normal dog will display anger at the sight of a distant enemy.

It has been found that cats and dogs which have survived decortication for some time are capable of showing the behavior characteristic of fear or terror.[234, 267, 269] The reaction is evoked by loud sounds of high pitch, but by no other kind of stimulus. The site of the subcortical mechanism responsible for this reaction pattern, which is entirely different from that of rage, has not been delimited. That the hypothalamic region may be concerned is suggested perhaps by its occurrence in a decorticate cat and dog from which the greater part of the striatal complex and the thalamus had been removed.

The Relation of the Hypothalamus to the Functions of the Pituitary Gland

From a physiological point of view the most significant feature of the close anatomical relationship between hypothalamus and hypophysis is the system of nerve fibers which join the two structures. As indicated in the anatomical part of this chapter, the hypothalamico-hypophysial system is the means whereby certain functions of the pituitary gland are brought under nervous control. The general functions of the hypophysis as an endocrine gland are discussed in other sections of this book. We shall take up here only those which are under nervous control.

The Neurohumoral Control of Water Balance.—It has long been recognized that lesions of the pituitary gland are likely to be followed by a condition known as *diabetes insipidus* and characterized by the drinking of large quantities of water (polydipsia) and the elimination of excessive amounts of very dilute urine (polyuria). The discovery that the posterior lobe of the pituitary contains an antidiuretic substance led to the belief that diabetes insipidus is a deficiency disease due to withdrawal from the blood of a hormone which acts to maintain a normal output of urine by the kidneys. Confusion entered this

field of investigation when it was found (1) that removal of the contents of the sella turcica may not lead to diabetes insipidus and (2) that lesions of the hypothalamus may produce permanent marked polyuria and polydipsia. But within recent years a considerable elucidation of this perplexing subject has been effected by the work of a number of investigators, especially Ranson and his co-workers.[244, 257] The explanation lies in the discovery of the control of the neurohypophysis by the hypothalamico-hypophysial system of nerve fibers and the proof that the antidiuretic principle of the pituitary has its origin in the neurohypophysis only and is not, as had been supposed, a product which enters the neural lobe after it has been formed in the glandular pars intermedia.[244, 257]

Ranson and his group of co-workers have shown quite conclusively in cats and monkeys that diabetes insipidus regularly follows restricted hypothalamic lesions which interrupt the supraopticohypophysial tracts bilaterally. Injuries of the hypothalamus which fail to do this are not productive of disturbances in water metabolism. These facts exclude the notion that polyuria of hypothalamic origin is due to nervous effects upon the kidney exerted through descending pathways. The intensity of the experimental diabetes insipidus is proportional to the degree of interruption of the supraopticohypophysial tracts; more than half the fibers must be destroyed before the intake and output of water increase (Fisher, Ingram and Ranson[244]). Degeneration of the tuberohypophysial tract, caused by lesions of the hypothalamus which destroy its origin, is not followed by diabetes insipidus.

It has been found that removal of the neural lobe or transection of the stalk below the median eminence may result in only a transient polyuria. The explanation of this apparently lies in the fact that the median eminence and infundibular stem, as well as the neural lobe, contain cells which elaborate the antidiuretic hormone. These parts of the neurohypophysis are evidently innervated by the fibers of the supraopticohypophysial system, for they atrophy after destruction of the supraoptic nuclei. Ingram and Fisher have found that complete removal of the neurohypophysis, including the infundibular stem and median eminence but leaving the hypothalamus intact, causes diabetes insipidus. The validity of the view that the hypothalamus regulates the secretory activity of the neural division of the pituitary was very considerably strengthened when it was discovered that the antidiuretic potency of extracts of the atrophied posterior lobes (atrophied neural lobe with normal pars intermedia) of cats with diabetes insipidus is reduced to about one-sixteenth of that of glands from normal animals.

It can be concluded that under normal conditions the anterior hypothalamus exerts a tonic excitatory action on the elements of the neurohypophysis which secrete the antidiuretic hormone. This influence is exerted through the projection of fibers from the supraoptic and other anterior hypothalamic nuclei. In all probability normal fluctuations in the level of antidiuretic hormone in the blood are produced by alterations in the tonic discharge of impulses over these fibers, but nothing is known of this aspect of the matter. The control of the supraoptic discharge may be nervous or it may be due to changes in the composition of the blood. The unique vascularity of the supraoptic nucleus suggests the operation of the latter factor.

The Relation of the Hypothalamus to the Gonadotropic Functions of the Anterior Lobe.—The pars distalis of the pituitary is responsible for the maintenance of a normal

state of the testes and ovaries and for the cyclical phenomena shown by these organs (see Chapter LXXIII). It exerts these effects through the production of the gonadotropic hormones. In all animals removal of the pars distalis leads to atrophy of the gonads and cessation of such periodical changes as ovulation (and menstruation in the case of those animals which show that phenomenon). A normal functional and structural condition of the ovaries can be restored in hypophysectomized females by administration of the gonadotropic hormones. One of these, the follicle-stimulating principle, causes the development of follicles; the other, the luteinizing hormone, leads to luteinization of the ovary and formation of corpora lutea. In most animals ovulation followed by the development of corpora lutea can be provoked by injections of the luteinizing factor and this is the basis of certain pregnancy tests. With this very brief outline of the functional relationship between the pituitary and the ovaries we can proceed with a consideration of the possible role played by the hypothalamus in regulating the gonadotropic functions of the pars distalis.

There is much evidence that among various groups of birds and mammals neural factors are involved in the control of the hypophysial gonadotropic functions (see Brooks[238]). The existence of the hypothalamico-hypophysial system of fibers provides a basis for supposing that the hypothalamus may influence this aspect of pituitary function. The only direct proof of such a control has been furnished by experiments on rabbits. This species, together with ferrets and cats, is unique in that the females ovulate only in response to the sexual excitement attending coitus; in all other mammals ovulation occurs "spontaneously" without any specific external stimulus. In the rabbit, cat and ferret a special or excess activation of the pars distalis seems to be necessary to induce ovulation. A study by Brooks[237] showed that the integrity of the pituitary stalk is necessary for the occurrence of ovulation in the rabbit. After severance of the stalk rabbits fail to ovulate in response to mating no matter how great the stimulus. This evidence has been supplemented by finding that electrical stimulation of the hypothalamus produces ovulation in rabbits, but only if the stalk is intact (Westman and Jacobsohn).[238] But it has not yet been determined which nuclear groups are involved in this reaction. In the normal course of events they are presumably activated by a neural stimulus connected with sexual excitement. At present we have no reason to believe, except on the basis of analogy, that in spontaneously ovulating forms the hypothalamus or any other part of the central nervous system is involved in the control of ovulation. It can only be said that while stalk section does not interfere with ovulation in many species, the association of certain abnormalities of the gonads and other parts of the reproductive system with various hypothalamic lesions in man suggests that this part of the brain is involved in maintaining the sexual functions of the pituitary.

The available anatomical evidence furnishes only fair support for the theory of neural mediation of hypothalamic influence on the pars distalis. Brooks[237] was able to show that in the rabbit a few fibers enter the anterior lobe from the pituitary stalk, and Brooks and Gersh[239] found a greater number in young rabbits and rats. Nevertheless the fact that the effect of stalk transection, in abolishing the capacity of rabbits to ovulate, cannot be attributed to interference with the blood supply of the pituitary (Brooks and Gersh[240]) or to any disturbance of the normal functions of the gland except its activation at the time of coitus (Brooks[237]) puts great emphasis on the importance of the fibers which do enter the pars distalis from the hypothalamus.

Adiposity.—In many of the earlier hypophysectomies carried out on animals there resulted not only genital atrophy but also adiposity. The condition had every resemblance to the clinical state known as the adiposogenital syndrome (Fröhlich's syndrome). At the time both the experimental and clinical conditions were attributed to injury or removal of the pituitary gland. In the light of subsequent work there can be no doubt that the genital atrophy was due to removal of the pars distalis. There remains some doubt as to the cause of the adiposity. P. E. Smith[262, 263] showed that in rats hypophysectomy is not followed by adiposity unless there is some coincidental damage to the hypothalamus. Injuries of the hypothalamus without direct involvement of the pituitary do not, however, always result in adiposity. In fact Ranson[257] states that only one case of adiposity has occurred among the several hundred animals which have been studied in his laboratory after being subjected to hypothalamic lesions of all sizes and positions. The evidence available is conflicting, and it would be premature at present to draw any definite conclusions. It can only be said that we seem to be justified in suspecting that the hypothalamus has some relationship to the control of fat metabolism.

Other Possible Functions of the Hypothalamus

A number of functions besides those discussed above have been attributed to the hypothalamus. Some of these assumptions have not been substantiated or have been contradicted by subsequent experimental tests. The present status of most of them is such that it is wise to withhold judgment concerning their validity. The more important may be given brief consideration here.

The view that the hypothalamus plays a part in the *control of carbohydrate metabolism* has been subjected to a great many experimental explorations, but no definite decision has been reached. In a recent review of the evidence for and against this hypothesis Long[251] concludes that while it has not been proved correct, "the available evidence does not entirely dispose of the possibility that some measure of influence may not yet be found."

The evidence that the hypothalamus is concerned in *sleep* will be discussed in Chapter XXI. It is perhaps of interest to point out here that in laboratory animals somnolence or hypersomnia is one of the most conspicuous results of large lesions in the caudal part of the hypothalamus. Hypersomnia is also very likely to occur in patients whenever hypothalamic functions are depressed by tumors, inflammatory processes or surgical interventions. It has been suggested (Ranson; Harrison[320]) that the hypothalamus exerts an influence in the induction of sleep which is an entirely negative one. This view is based on the evidence that emotional excitement or increased activity results from hypothalamic activation, and it involves the concept that cessation of hypothalamic activity predisposes the individual or the animal to fall asleep.

The relation of the hypothalamus to *sexual behavior* has recently attracted some attention. The fact that decorticate female cats are capable of displaying the full behavior pattern characteristic of estrus when they go into "heat" either spontaneously or as a result of injecting estrogenic substances shows that this form of behavior is managed subcortically.[234, 235] And the further fact that true estrous responses cannot be evoked in spinal or bulbospinal cats indicates that the essential central mechanism lies above the lower mesencephalon.[235] Magoun and Bard[235] showed that the full pattern of estrous behavior can be obtained in cats with complete destruction of either the middle or caudal third of the hypothalamus and pointed out that in the case of the caudal lesions all known descending connections of the hypothalamus had been interrupted. Recent reports from Ranson's laboratory have indicated, however, that in guinea pigs lesions of the more rostral portions of the hypothalamus abolish the capacity to exhibit reactions typical of estrus.

CHAPTER XVIII

THE SENSORY CENTERS OF THE BRAIN

Sensory experience and the recognition of the quality and location of stimuli acting upon the receptors of the body depend upon the arrival of impulses at certain stations in the brain which correspond to the receptors in question. Knowledge concerning the location of the centers involved in the perception of sensations arising from each kind of receptor and from each part of the body has been gained to a considerable extent by inference from the anatomical arrangements of the fibers connecting the sense organs with the various parts of the brain and from studies of the reactions of animals which have had certain parts of the brain removed. But this information is of limited value, since we can learn about a sensation directly only through the verbal report of the person who experiences it. Although important information concerning the sensory centers of the brain has come from the clinic, it has on the whole lacked the detail and decisiveness of the less easily interpreted results of animal experimentation. This is due to two facts: the impossibility of performing extensive experimental procedures on human beings, and the difficulty in determining the true extent of an injury or pathological process.

THE THALAMUS

The thalamus is the great sensory ganglion of the brain stem; it receives and forwards all sensory impulses destined for the cerebral cortex. The final synaptic junction and relay station for the transmission of corticipetal impulses lies in this portion of the diencephalon. Thalamocortical fibers from one side of the thalamus do not cross to reach the cortex of the opposite hemisphere. It has long been known that the thalamus receives fibers from the cerebral cortex; in general the corticothalamic fibers from any one cortical area end in the same thalamic nucleus which projects to that area. Their function has not been established, but there is some indication that they may play an important role in the development of sensory experience.

The thalamus is by no means a functionally homogeneous unit. It is a paired structure, each half of which is made up of at least three functionally distinct groups of nuclei, and each of these doubtless plays a different role in the integration of afferent impulses and sensation.

The Thalamic Nuclei and Their Connections

On each side the thalamus receives six afferent projections. Two of these, the optic tract and lateral lemniscus, carry the impulses concerned in vision and audition. The other four are the somatic afferent tracts from the spinal cord, medulla oblongata, and cerebellum: the spinothalamic tract, the medial lemniscus from the gracilis and cuneate nuclei, the brachium conjunctivum from the dentate nucleus, and the trigeminal lemniscus. While it has long been known that the optic tract and the lateral lemniscus terminate in the lateral and medial geniculate bodies, respectively, it has been established only comparatively re-

cently that each of the somatic sensory projections also ends in a fairly discrete portion of the thalamus. Further, just as the two geniculate bodies project to specific areas of the cerebral cortex, so the several thalamic nuclei which receive different somatic sensory tracts also project to different parts of the cortex. The demonstration of this fact, which has important physiological connotations, is due largely to the work of Le Gros Clark and the studies of Walker carried out chiefly on monkeys. Since there is great similarity between the thalamic arrangements in monkeys and those in the chimpanzee, it seems reasonable to suppose that the results can be applied, with but slight modification, to the human thalamus. The details of thalamic organization may be sought in the monograph by Walker[313] or in Fulton's excellent account of the structure and function of the thalamus (Fulton,[124] Chapter XIV). Only the more salient features of the arrangement will be given here.

The connections of the various parts of the thalamus can be determined by several anatomical methods. The thalamic endings of each of the ascending pathways may be judged by interrupting one or another of these tracts surgically, allowing the animal to live from two to three weeks, then killing it and applying the Marchi technique which visualizes degenerating nerve fibers (myelinated). The same method may be employed to trace the thalamic projections to the cerebral cortex; in this case a restricted lesion is made in the thalamus. Because of the difficulties and vagaries of the Marchi method a better way of following the thalamocortical projections has been adopted, particularly by Clark and Walker. This is based on the fact, discovered by Gudden and Nissl, that a cortical removal, by interrupting the distal portions of the thalamocortical fibers, leads to a *retrograde degeneration* of the corresponding cell bodies in the thalamus. This change, which is permanent and can be made out in serial sections cut through the thalamus, permits a delimitation of the sources of the various thalamic projections.

The Three Major Groups of Thalamic Nuclei.—On the basis of its anatomical organization and connections the thalamus can be most appropriately subdivided into three main nuclear groups as follows:

1. *Nuclei With Subcortical Connections Only (Midline, Intralaminar and Anterior Ventral Nuclei).*—These are the parts of the thalamus which do not degenerate when the cerebral cortex is completely removed and therefore are regarded as having no direct cortical projections. They are connected with other parts of the thalamus and also with extrathalamic subcortical regions. The midline group of nuclei, which lie in the middle portion of the thalamus close to the upper part of the walls of the third ventricle, are relatively constant throughout the mammalian scale and accordingly are sometimes called the paleothalamus. Little is known of their afferent connections, but according to Walker[313] they receive fibers from the medial lemniscus and spinothalamic tracts. They project to the hypothalamus. It is generally assumed that they have something to do with visceral sensibility or visceral reactions. The intralaminar nuclei include the centromedian nucleus which probably projects to the corpus striatum.

2. *The Cortical Relay Nuclei (Anterior and Ventral Nuclei and the Geniculate Bodies).*—All these receive fibers from primary or secondary sensory neurons and project to the cerebral cortex. After removal of the cortex they degenerate almost completely.

The *anterior nuclei* receive afferent fibers from the mammillothalamic tract and therefore are probably played upon by impulses from olfactory centers. They project to the gyrus cinguli which is found on the medial cortical surface of the hemisphere.

The various parts of the *ventral nucleus,* with the exception of the anterior ventral nucleus (see above), receive the major ascending tracts mediating somatic sensibility. The projections of these fiber systems in the ventral nucleus are relatively distinct. This part of the thalamus is divisible into the *lateroventral nucleus,* which receives the fibers of the brachium conjunctivum, and the more caudally situated *posteroventral nucleus* where the medial and trigeminal lemnisci and the spinothalamic tracts terminate. The posteroventral nucleus in turn has two more or less distinct parts, the *nucleus ventralis posterolateralis* and the *nucleus ventralis posteromedialis.* The fibers from the cord and from the dorsal column nuclei end in the former, those from the fifth nerve nuclei in the latter. Thus the head and face have a more medial representation in the thalamus than the arm and leg, a topographical relationship which is the reverse of that in the cortex (see Figs. 70 and 71). The lateroventral nucleus projects to the *precentral motor areas* (areas 4 and 6) of the cerebral cortex. It thus serves to relay impulses of proprioceptive origin from the dentate nucleus of the cerebellum to the parts of the cortex which have to do with muscle movements and tone; it is concerned with a form of proprioceptive sensibility which does not cross the threshold of consciousness. The two divisions of the posteroventral nucleus project to the *postcentral gyrus* or sensory cortex (areas 3, 1 and 2) to which they relay impulses originating in exteroceptors and proprioceptors; these impulses give rise to the various modalities of somatic sensation.

The *lateral geniculate body,* which is a relay station for visual impulses, receives fibers from the retinae of the two eyes and projects only to the *area striata* (area 17) of the same side (Fig. 74). The *medial geniculate body,* lying between the lateral geniculate and the cerebral peduncle, mediates auditory impulses which come from the cochlear nuclei of both sides by way of the lateral lemniscus. It projects to the auditory cortex of the temporal lobe. The investigations of Polyak[305] and of Walker[313] seem to have settled the long debated question of the exact locus of the auditory projection in the primate cortex; this turns out to be in the monkey a small area on the superior surface of the first temporal convolution which corresponds to cortex on the transverse temporal gyrus of Heschl in the human brain.

3. *Association Nuclei (Lateral and Dorsomedial Nuclei and Pulvinar).*— Comparative studies show that these nuclei are of recent phylogenetic development. They receive few if any fibers from the main afferent tracts but project to the so-called association areas of the cerebral cortex; they degenerate when these parts of the cortex are removed. These facts suggest that they subserve higher sensory functions. The *lateral nuclei* project to the posterior part of the parietal lobe (areas 5 and 7), the *dorsomedial nucleus* to the prefrontal region (areas 9, 10 and 12) and the *pulvinar* to an indiscriminate area which includes contiguous parts of the temporal, parietal and occipital lobes, but not the area striata. This group of nuclei receive impulses from the relay nuclei, and doubtless send them on to the cortex modified in sequence and distribution.

Sensory Functions of the Thalamus

The organization of the thalamus and of the fiber systems from the relay nuclei to the cortex is in part at least such as to maintain a rigorously predetermined relation between the spatial distribution of a peripheral stimulus and the locus of the primary cortical reaction. As illustrated in Fig. 73, impulses set up

by a tactile stimulus applied to a single cutaneous point invade a discrete cortical area, and there is evidence that the same relationship between periphery and cortex holds for the visual system. It is evident therefore that the posteroventral nucleus and the lateral geniculate body do not interfere with the point-to-point relation of the periphery to its projection on the cortex. On the other hand, detouring of impulses through the thalamic association nuclei doubtless leads to the bombardment of different parts of the cortex by impulses which may very well condition the effects of the primary volley or evoke effects which are independent of those produced by directly relayed impulses. We are here confronted by a most interesting question which to date has not been elucidated.

A problem which has been given much attention is whether the thalamus mediates any form of sensation independently of the cortex. When a thalamic lesion affects the sensory fibers caudad of their terminations in one of the thalamic nuclei the sensory loss is identical in quality with that which develops as a result of interruption of impulses in the ascending tracts at a bulbar or mesencephalic level. Because of decussation of the sensory tracts in cord and medulla sensation is chiefly affected in the opposite side of the body.* The extensive clinical observations of Head and Holmes[291] led them to assign a very important part in the origin of certain aspects of sensation to a thalamic mechanism which they termed "the essential organ of the thalamus." This concept was based on the *thalamic syndrome* of Déjerine and Roussy, a condition which usually results from destruction of the caudal portions of the ventral and lateral nuclei by occlusion of the thalamogeniculate artery. A severe sensory loss is combined with an overreaction (hyperesthesia) to certain forms of stimuli, and paresthesias of the parts affected. So long as some sensory impulses, especially those which are capable of exciting discomfort, are still able to impinge on consciousness, the affected half of the body (contralateral to the side of the lesion) gives rise to more profound reactions than the normal parts. For example, a patient afflicted with the thalamic syndrome will exclaim, "Something is happening to me, I am being hurt," instead of "You are sticking a pin into the back of my hand," because he fails to recognize the distinctive characters of the stimulus in question. In addition, however, certain stimuli which do not ordinarily produce any discomfort, may evoke an exaggerated response in sensation. The movement of cotton wool over the skin may give rise to excessively unpleasant sensations. Head advanced the idea that such effects are due to lesions which release the essential center of the thalamus from an inhibitory control exerted by the cortex, and suggested that this center is mainly concerned with the affective side of sensation. The French school of neurologists have opposed this theory on the ground that it is not damage to the corticothalamic fibers but actual involvement of the thalamus itself which produces the sensory overreaction. Also Dusser de Barenne[310] has called attention to the fact that, if the hypothesis were correct one should expect similar disturbances to appear after lesions of the sensory cortex which involve the corticothalamic neurons and which would lead to degeneration of the ventrolateral nuclei; this, however, is not found. It has been suggested that the thalamus normally modulates sensory messages and that this action depends on the normal relationship between the ventral (relay) and lateral (association) nuclei.

*It was shown by Probst that some fibers of the medial lemniscus cross the midline to enter the opposite half of the thalamus; this arrangement may account for instances of bilateral cerebral (thalamic and cortical) representation of the sensibility of one half of the body.

Significant results bearing on the problem of the sensory functions of the thalamus have been obtained in animal investigations by the method of local strychninization. As will be related below, Dusser de Barenne has shown that the local application of strychnine to certain parts of the cortex in cats and monkeys produces signs of marked hypersensitivity (hyperesthesia, hyperalgesia, parasthesias) of the skin to tactile, painful and thermal stimuli, and of the deeper structures to pressure. Local strychninization does not evoke motor responses. Because of the high molecular weight of the alkaloid it does not readily diffuse from the point of application. Dusser de Barenne and Sager[284] (see also Dusser de Barenne[310]) found that injection of a small quantity of a weak solution of strychnine into the thalamus of the cat evokes a typical complex of symptoms which is exactly the same as the syndrome of local cortical strychninization. The symptoms are obtained from the ventral, lateral, and medial thalamic nuclei. This fact does not necessarily mean that the medial nuclei have the same sensory functions as the ventrolateral group of nuclei, for, as Dusser de Barenne has stated, the method has one great limitation: "In producing the maximum of sensory functions it blurs finer functional differentiations." The sensory disturbances evoked by strychninization of the thalamus occur on cutaneous stimulation of either half of the body, but the strongest are evoked from the contralateral side. Deep sensibility appears to have only a contralateral thalamic representation. Removal of the cerebral cortex does not alter the result in acute experiments. When the experiment is done on an animal which has long survived removal of the cortex of one cerebral hemisphere and in which the ventrolateral nuclei of the ipsilateral half of the thalamus have consequently undergone secondary degeneration, strychninization of the other thalamus produces the typical bilateral disturbances of cutaneous sensibility and the contralateral disturbances in deep sensibility. From this the conclusion has been drawn that "the skin of both halves of the body and the deep structures of the contralateral half of the body are sensorially represented in each thalamus." He points out that this may account for the observation that in cases of the thalamic syndrome the abnormal responses to cutaneous stimulation are often transient while impairment of deep sensibility is more marked and of longer duration. The work of Dusser de Barenne and Sager also revealed the existence in the thalamus of distinct, but partially overlapping, representations of three parts of the body—face, arm and leg. No finer subdivisions of the representation were indicated by their results.

That a high level of functional integration is attained by the thalamus, even in the cat, is indicated by the fact that the symptoms of local strychninization are the same immediately after removal of all cortex. Of course when the inevitable secondary degeneration has set in (as in chronic experiments) the representation is obliterated.

Cases of complete removal of the cortex of one hemisphere (the right) have been reported by Dandy,[276] Gardner[289] and other neurosurgeons. On the affected side these patients regain appreciation of touch and pin-prick but without accurate localization and lose permanently all forms of deep sensibility, such as recognition of position and movement. What is the basis of the appreciation of the sensory modalities that remain? One possible answer is that the thalamus on the side of the ablation is capable of subserving relatively crude sensations even after the inevitable degeneration of the relay and asso-

ciation nuclei. Another explanation is that the sensibility of each side of the body is represented bilaterally in thalamus and cortex. The fact that unilateral chordotomy may not relieve pain from an extremity and the observation of Bychowsky and Eidinow[275] that careful examination of patients with unilateral cerebral lesions reveals bilateral sensory disturbances would support the second of these explanations. The studies of Dusser de Barenne and Sager on cats and monkeys mentioned above also indicate a bilateral thalamic representation. Apparently only the modalities of exteroceptive sensibility are bilaterally represented; proprioceptive sensibility is represented only in the contralateral thalamus and cortex.

THE SENSORY AREAS OF THE CEREBRAL CORTEX

The Area of Cutaneous and Deep Sensibility (Somesthetic Area).—Impulses giving rise to cutaneous and deep sensibility which pass from the thalamus to the cortex divide themselves into five main afferent streams, which may be affected by cortical lesions more or less independently. These comprise impulses concerned with: (1) postural recognition and appreciation of passive movement; (2) tactile localization; (3) the tactile recognition of differences in weight of a test-object and the distinguishing of differences between two weights applied to the supported hand; (4) spatial discrimination and the appreciation of the size, shape, and form in three dimensions (stereognosis); (5) recognition of differences and similarities in temperature. The outstanding feature of cortical sensibility is the recognition of fine detail in sensation, enabling us to perceive not only the presence of a stimulus and its gross quality, but also to discriminate between stimuli of different intensities, to recognize the shape, size, weight, and texture of the stimulating object, and to recognize the position of the hand as it explores its surface. Thus if a glass of hot water is placed in the hand of an individual whose cortical sensory area corresponding to the hand is damaged, he will recognize the contact of the object and will know that it is unpleasantly hot. He will be unable, however, to perceive the roundness, size, or weight of the vessel, to know how hot it is, or to recognize the position of the hand which grasps it. An outstanding effect of lesions within the somatic sensory area of the cortex is the variability of the responses to sensory tests. This peculiarity indicates that the cortex enables attention to be focussed upon those changes evoked by sensory impulses. The patient therefore reports on the effects of a series of stimuli in a manner which appears to be untrustworthy, and it is usually impossible to establish a threshold for any form of somatic sensory stimulation.

Several different methods have been employed in attempts to determine the position and extent of the cortical area subserving cutaneous and deep sensibility (the zone of somatic sensibility; the somesthetic area). Clinical studies of cortical lesions have on the whole supported the idea of a complete spatial separation of motor and somatic sensory areas. Over twenty-five years ago, Harvey Cushing, in the course of operations on the human brain carried out under local anesthesia, electrically stimulated, with the patients' consent, the convexity of the cerebral hemisphere. The patients, who were fully conscious, reported that they experienced definite sensory impressions when the postcentral gyrus was stimulated. These sensory experiences consisted of a sensation of

numbness, tingling, or tactile impressions (paresthesia). They were projected out to some specific part of the opposite half of the body, the region from which they seemed to come depending upon the part of the postcentral gyrus stimulated. No muscular groups underwent movement unless the precentral gyrus was stimulated, when no sensations were experienced by the patient except those which accompanied the change in the position of the part that was moved.

On the basis of a very large number of neurosurgical cases Otfrid Foerster[285] has described in terms of various architectonic areas of the human cortex the effects of electrical stimulation, the effects of irritation by pathological lesions, and the effects of partial or complete destructive lesions. Cushing's report that electrical stimulation of the postcentral convolution gives rise to paresthesias was confirmed. The gyrus appears to be divided into a large number of sensory

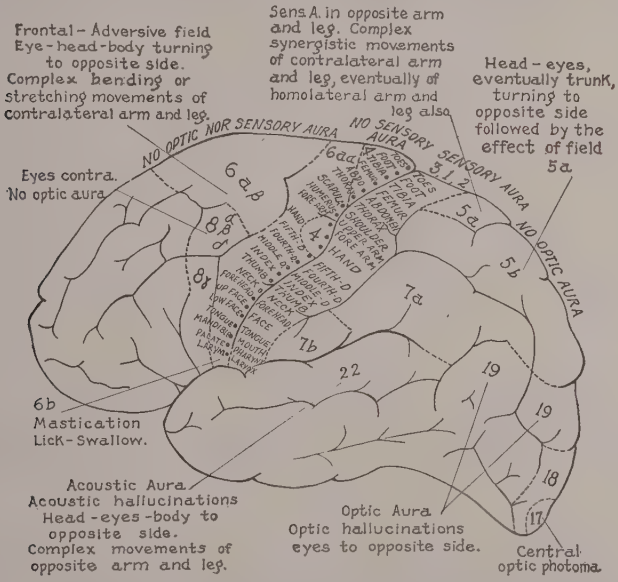

Fig. 70.—Diagram of the human cerebral hemisphere seen from the left side, illustrating areas whose electrical stimulation is followed by movement or sensation. The numbers of the areas are those of Vogt, which differ somewhat from those of Brodmann. (After Foerster and Penfield.) (From Herrick: An Introduction to Neurology. W. B. Saunders Co.)

foci, each of which represents contralaterally a special segment of the limbs or a special part of the body (Fig. 70). The arrangement is in the same general order as is the motor representation in the precentral gyrus. The lowermost parts of the body are represented near the medial surface of the hemisphere, the uppermost parts close to the Sylvian fissure. The representation of somatic sensibility brought out by electrical stimulation was confirmed, in Foerster's experience, by the results of focal lesions in the postcentral gyrus. A sensory effect consisting of widespread paresthesias and sometimes pain appearing simultaneously in the trunk and limbs of the opposite side, and sometimes also in the bladder and rectum, was obtained from stimulation within the upper

rostral part of the superior parietal lobule. Specific somatic sensory effects were not obtained from stimulation of other parts of the cortex.

The loss in somatic sensibility which follows destructive lesions of the postcentral convolution in man is recovered from to a considerable degree. It is probable that this result is partly due to a certain amount of ipsilateral representation so that the intact cortex of the other hemisphere may substitute for the impaired hemisphere. It is known, however, that considerable recovery of sensation may occur after bilateral postcentral lesions. This may be explained by the fact that the somatic sensory area of the cortex is in reality far more extensive than is indicated by the results of electrical stimulation in conscious patients. It is important to bear in mind that the application of a stimulating current to tissue of such histological complexity as the cerebral cortex can scarcely be expected to give the same result as the arrival of definitely grouped corticipetal nerve impulses.

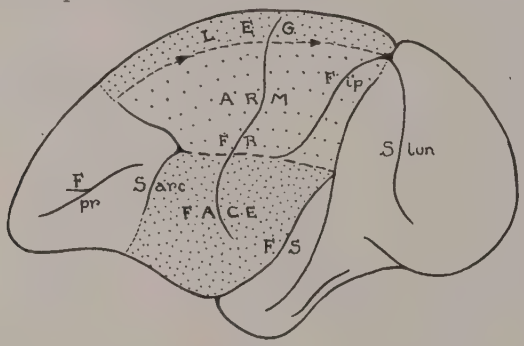

Fig. 71.—Sensory cortex on the convexity of the hemisphere in the monkey (Macacus) as revealed by the method of local strychninization (Dusser de Barenne[280]). The broken lines indicate the boundaries between the three subdivisions of the sensory zone. *F R* indicates the central fissure; *F S*, the Sylvian fissure; *F ip*, the intraparietal sulcus; *S lun*, the lunate sulcus; *S arc*, the arcuate sulcus. (From Dusser de Barenne: *Handbuch der Neurologie*, Berlin, 1926, J. Springer.)

Studies of the effects of cortical ablations in animals have not in general yielded decisive information concerning cortical sensory functions, for the only criterion of sensory disturbance is a change in some motor performance. Certain extirpation experiments in monkeys and other infrahuman primates have indicated that the representation of somatic sensibility is restricted to the postcentral gyrus. Woolsey and Bard,[268] however, in a study of the cortical management of the placing and hopping reactions of monkeys (see page 142), have been able to show that while removal of all cortex behind the central fissure completely eliminates the placing reactions, which are of tactile origin, it does not affect (except temporarily) the hopping reactions, which are proprioceptive in origin. This result suggests that at least one form of proprioceptive sensibility is dependent on precentral cortex.

There is now available a considerable body of evidence to suggest that the representation of cutaneous and deep sensibility in the cortices of primates is not confined to the postcentral gyrus. Dusser de Barenne[280, 310] has shown this in a striking manner by use of his method of local strychninization (see page 205). In the monkey the cortical area in which local application of strychnine

produces symptoms of hyperesthesia covers not only the postcentral cortex to the extent of the entire parietal lobe, but also the precentral cortex as far rostrally as the arcuate sulcus (Fig. 71). As in the case of the thalamus, the symptoms of sensory excitation produced by local strychninization on one side indicate that, so far as cutaneous sensibility is concerned, both sides of the body are represented in the sensory area of each cortex while deep sensibility is represented almost exclusively in the contralateral cortex. The action of strychnine fails to bring out the details of sensory localization which other methods have revealed. The zone is divisible only into leg, arm and face areas. Further, the method is apparently incapable of distinguishing the spatially distinct representations of the different qualities of somatic sensibility whose existence is strongly suggested, if not definitely demonstrated, by other modes of investigation. These are the limitations of the method. As already pointed out, strychnine, when locally applied to central nervous tissue, apparently brings out the maximum of sensory function, but in doing so it obscures the finer functional differentiations (Dusser de Barenne[310]).

Application of strychnine to a few square millimeters of the arm area of one cortex gives rise to the same hypersensibility as strychninization of any other similar fraction of that area. This fact may be interpreted in two ways: Either the skin of both arms is represented many times over on each cortex, or the strychninization of a very small area causes a spread of excitation through the whole of the representation of the arm. The first explanation is so incongruous as to be highly improbable: the second is reasonable, especially if it be extended to include an excitation of those portions of the thalamus in which the arm is represented. Dusser de Barenne showed that the typical syndrome appears on strychninization of a few square millimeters in the precentral portion of one arm area after the rest had been novocainized and the entire ipsilateral postcentral and contralateral pre- and postcentral arm areas had been extirpated. It has already been pointed out that after complete decortication local strychninization of the thalamus results in the same state of sensory hyperexcitability as is obtained by cortical application of the drug (Dusser de Barenne and Sager[284]).

The view that in the primate the cortical sensory area concerned in deep and cutaneous sensibility is more extensive than had been supposed is supported by recent anatomical investigation. After interruption of the thalamocortical fibers concerned in somatic sensibility at their diencephalic origin or close to it, Poliak[305] has traced their degeneration into the cortex of the monkey. His results show that "there exists a wide region of the hemisphere which receives fibers of thalamic origin and extends about equally, orally and caudally, from the sulcus centralis as well as over the internal face of the hemisphere where it reaches the sulcus cinguli." A narrow strip formed by the two walls of the central sulcus is the part which is most richly supplied with somatic sensory fibers from the thalamus. This focal zone is entirely buried within the central sulcus. The density of the cortical terminations of these sensory fibers becomes gradually less as one passes rostrally or caudally from the sulcus. There is a remarkable topographical agreement between the sensory zone delimited by Dusser de Barenne's strychnine method and that outlined by Poliak's anatomical studies.

A far more detailed picture of cortical sensory representation than any previously presented has been obtained as the result of the discovery that the application of a discrete tactile stimulus to a cutaneous area produces in the cortex of the anesthetized animal a well-localized potential wave (Marshall, Woolsey and Bard;[301, 302] Bard[268]). The features of the representation are more easily made out in the cortex of the monkey than in that of a carnivore. This is because of the larger size and more clearly defined spatial relations of the primate brain. The two parts of Fig. 73 show the representation of tactile sensibility in the monkey's cortex as revealed by the cortical potentials set up on stimulation of touch receptors in different parts of the contralateral half of the body.

A brief description of the experimental procedure will make clear the nature of the results obtained. After opening the skull and dura so as to lay bare the greater portion of the external surfaces of one or both cerebral hemispheres, small adjustable electrodes are brought in contact with the pial surface, one on a point within the somesthetic area, the other on an indifferent region such as the occipital cortex. Potential differences which develop between the electrodes can then be recorded by means of an amplifier and a cathode ray oscillograph. Mechanically discrete stimuli which are very brief in duration, low in frequency and close to the human threshold must be used to avoid the complications of spatial and

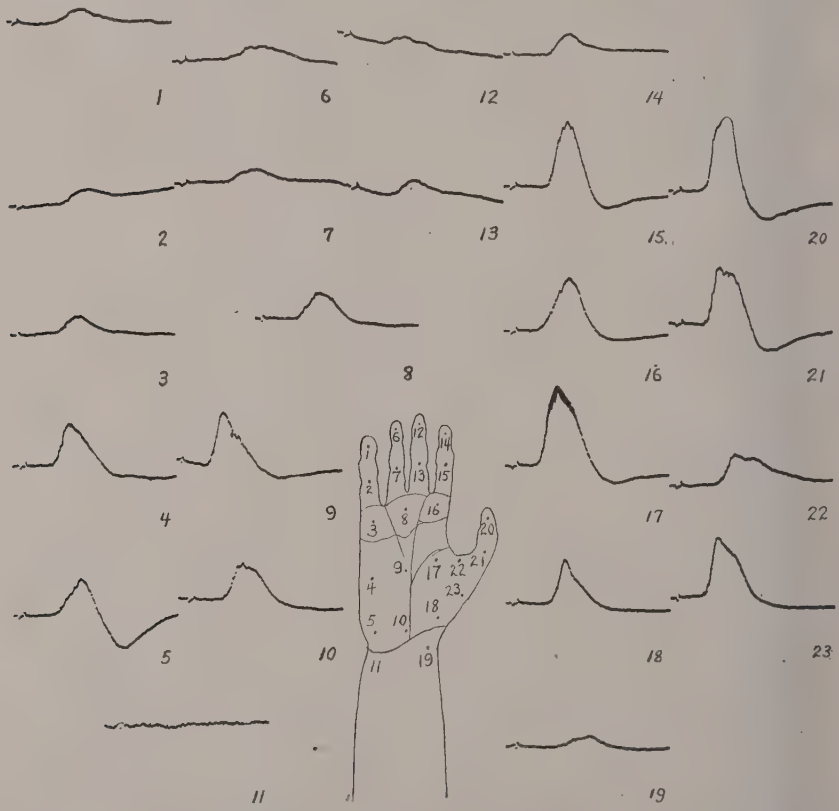

Fig. 72.—Surface positive potentials recorded from a single spot in the hand area of the left postcentral gyrus on light tactile stimulation of various points on the palmar surface of the right hand. Monkey under pentobarbital sodium anesthesia. Cathode ray oscillograph. Tips of small thread electrodes on pial surface. Indifferent electrode on occipital lobe. Upward deflection denotes that postcentral spot is electropositive to occipital spot (which does not respond). Small initial deflection signals brief contact of stimulating hair with the skin, a stimulus just above human threshold. Maximal responses from thumb and adjacent surfaces of palm and index finger. (From Marshall, Woolsey and Bard.)

temporal dispersion of afferent impulses. Stimulation is most effectively applied to hair-covered areas by a small camel's hair brush, to bare regions by the tip of a small von Frey hair or a cat's vibrissa. These objects are mounted on a lever arranged to move to-and-fro through a distance of about 0.5 mm. within a few milliseconds. The arrangement is such that this movement, and hence the stimulus, is signalled in the x axis of the cathode ray sweep (Fig. 72).

When the active electrode is placed on a cortical spot corresponding to the peripheral area stimulated a surface-positive wave follows each restricted tactile stimulus. The latency of this response, in milliseconds, averages 15 to 20 for toes, 8 to 11 for fingers and 5 to 9 for face. Although stimulation of a specific peripheral locus elicits responses over a cortical area of several square millimeters, one or more distinct spots of maximal potential can always be found. The site or sites of these can be determined only by moving the electrode in steps of a fraction of a millimeter. The size of the cortical area varies with the part of the body surface stimulated. Stimulation within a region of relatively low sensibility such as the back gives rise to potentials which are restricted to a very small cortical area, while stimulation of the thumb or great toe, where cutaneous sensibility is acute, produces potentials over a different but very much larger fraction of the somesthetic area. A general mapping of the entire Rolandic region can be achieved in twenty to forty hours in a single experiment on a monkey by exploring with the stimulator the entire body surface each time the active electrode is placed on one of a series of arbitrarily selected cortical spots. A more detailed picture is obtained when this procedure is carried out by systematically testing cortical spots which lie only one millimeter or less apart along rostrocaudal and transverse coordinates. Fig. 72 shows the potentials recorded from a single cortical spot when light tactile stimuli are applied to various points on the palmar surface of the hand. It is evident from the sizes of the waves that the thumb and adjacent surfaces of the palm and index finger are represented. A slight change in the position of the electrode will entirely alter the relationship of the waves to one another, and with a further shift in position the electrode will fail to pick up any potentials when the hand is stimulated, for it is now on the cortical representation of some other region. In the two parts of Fig. 73 are shown the combined results of mapping experiments carried out on a series of monkeys.

The representation shown by the cortical potentials which follow light tactile stimulation of the skin is a stable arrangement. No shifting of points occurs in the course of an experiment and the map derived from one animal is almost identical with that from any other monkey. Under the conditions of the experiment the representation of tactile sensibility, at least, appears to be confined to the histological fields 3, 1 and 2 of Brodmann. Inspection of Fig. 73 shows that over this area the parts of the contralateral body surface are represented in an orderly sequence. In the case of the lower extremity this sequence clearly reflects the metameric origin of the dermatomes; the arrangement is in the order of the spinal innervation, not in the order—hip, thigh, knee, leg, ankle, foot, toes. No evidence of bilateral representation was secured except in the case of the face, nor were maximal potentials in response to tactile stimulation found precentrally. It must be recognized, however, that this method may not reveal the entire cortical representation of tactile sensibility. Anesthesia doubtless represses spread of effects through the cortex and it may possibly block the entry of afferent impulses into the ipsilateral cortex. Nevertheless, there can be little doubt that whatever functional variations may characterize the total cortical response to a tactile stimulus, they are based on a highly stable anatomical substratum which is functionally demonstrable in terms of these potentials. Some evidence has been obtained that a strong stimulus of the kind which would give sensations of pressure or pain, or both, may evoke potentials in the somesthetic areas of both cortices.

At present little can be said concerning the origin of these evoked cortical potentials. They are apparently independent of the outer layers of the cortex, for they are not modified by thermocoagulation of these. It is possible that they represent the summed action potentials of the terminations of thalamocortical fibers. On the other hand, they may arise in the somata of cortical neurons. The fact that they are positive in sign for the most part and sometimes diphasic (Fig. 72) gives scarcely any information on this point; the sign of any potential led from a tissue depends chiefly on the orientation of the leading-off electrodes.

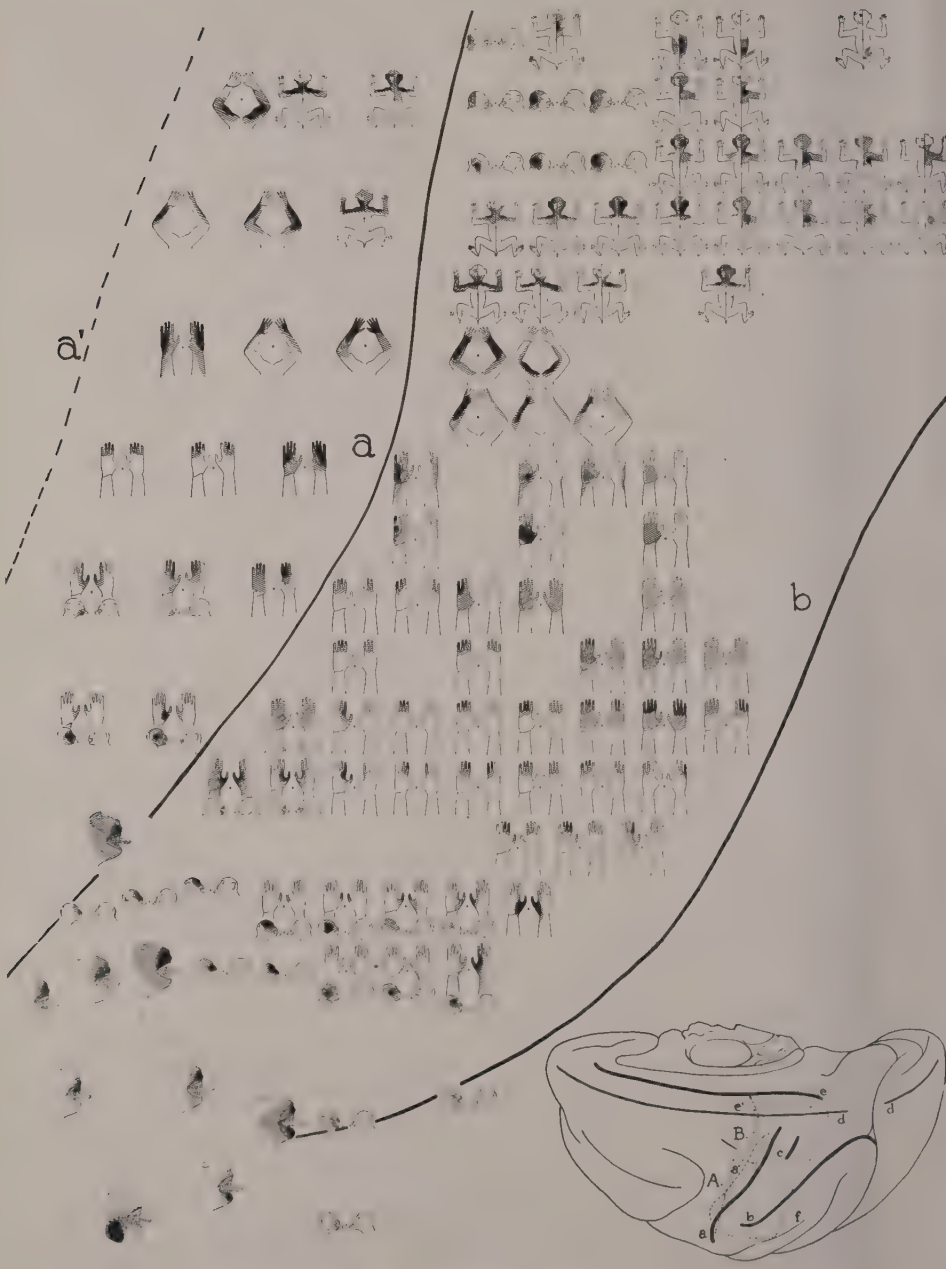

Fig. 73*A*.—(See legend on page 214.)

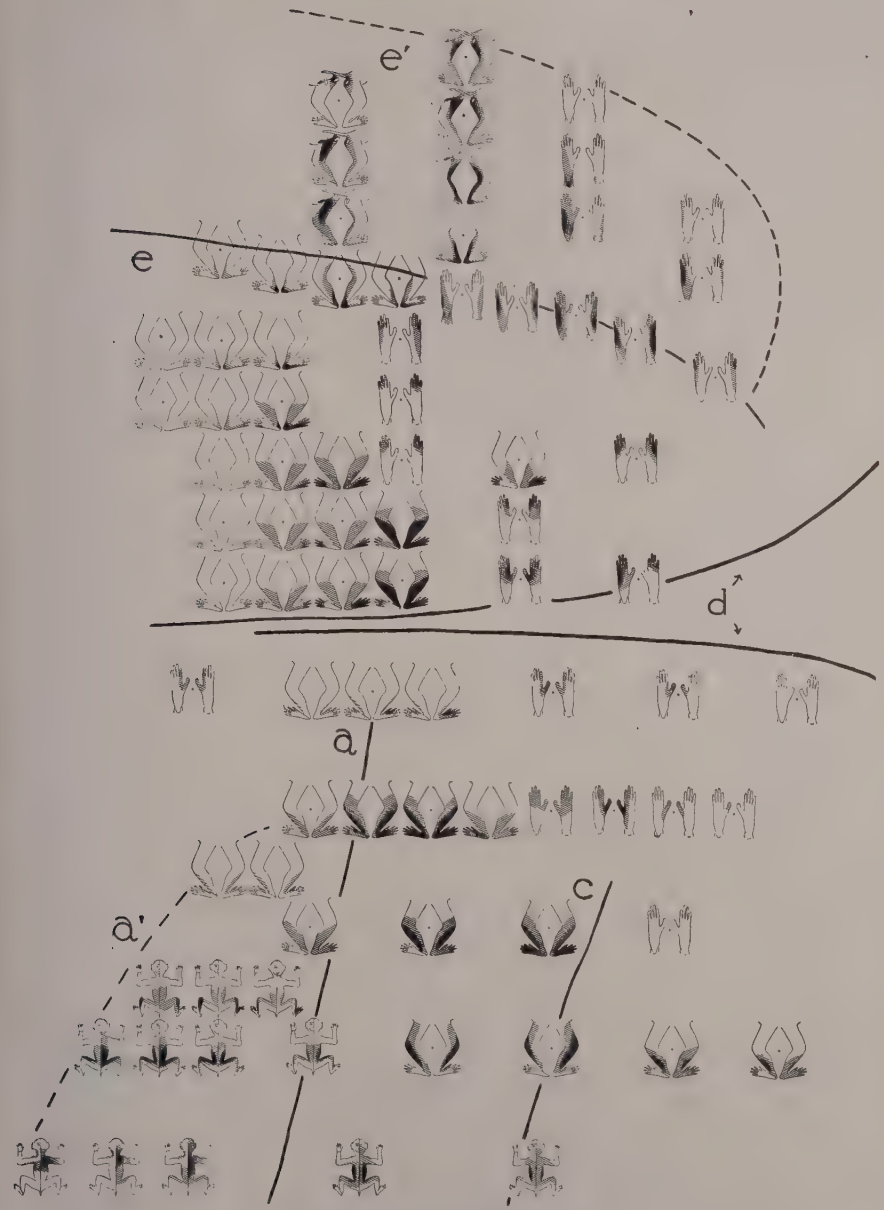

Fig. 73*B*.—(See legend on page 214.)

The Olfactory and Gustatory Areas.—Our present concept of the olfactory mechanisms of the brain is derived almost entirely by inference from the organization and connections of the rhinencephalon. The subject remains predominantly a morphological one, and the student can find the greater part of what is known of it in textbooks of neuro-anatomy. The cortical portions of the olfactory brain are phylogenetically old and are therefore spoken of as *archicortex* and *paleocortex*. In the lower vertebrates this is the only cortex. The olfactory cortex is distinguished from the *neocortex* which has developed later, in connection with nonolfactory systems. The rhinencephalon makes connections with the neocortex, chiefly through the mammillothalamic tract and the anterior nuclei of the thalamus which project to the gyrus cinguli. From this area on the medial surface of the hemisphere impulses originating in the olfactory centers may spread to other parts of the neocortex. In this connection it should be mentioned that recently W. F. Allen,[266] by employing the conditioned reflex technique, has shown that the electrically excitable part of the neocortex (motor area) is necessary for the establishment and retention of specific learned responses to olfactory stimuli. From this it may be concluded that the rhinencephalon can act upon and through the neocortex.

Little is known of the mechanisms of the brain which mediate either gustatory responses or the sense of taste. A cortical area for taste has been variously located in three regions: the temporal lobe, the insula, and the parietal lobe (see the review by Börnstein[270]). The best evidence[270] indicates that the gustatory area is situated in the parietal lobe at the foot of the postcentral gyrus, a location which places it just behind the motor chewing area of the precentral gyrus (Fig. 70).

The Auditory Area.—The projection of the medial geniculate body to a small area in the superior part of the temporal lobe has already been described (page 203). Stimulation of this region in conscious patients causes them to experience buzzing and roaring sounds, a result which is not obtained from stimulation of other parts of the cortex (Penfield and Gage). In man removal of one temporal lobe has very little effect on hearing, and the cases of complete unilateral ablation of the cortex mentioned above showed no easily detectable impairment in hearing. Even bilateral temporal lobectomy in man leaves a measure of audition, and in the monkey and baboon this operation appears to do little more than reduce auditory acuity and the ability to localize accurately the source of a sound (Fulton,[124] page 369). Wholly decorticate cats and dogs show marked auditory responses; both Dusser de Barenne[279] and Bard and

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Fig. 73.—*A* and *B*. Tactile sensory area of monkey's cerebral cortex as indicated by cortical potentials. In each of the small figures (consisting of a pair of hands, arms, feet, etc.) is shown by shading the cutaneous area which on tactile stimulation gives rise to potentials at the cortical spot indicated by the position of the small figure on the larger diagram. In each case (except the head) the right half of the figure represents the dorsal surface, the left half the ventral surface of the part illustrated. Largest potentials were evoked by stimulation of the central portions of the solidly shaded areas. *A* and *B* each show approximately one-half of the total area. Their positions with respect to the general topography of the cortex are indicated in the inset which is a diagram of the dorsolateral and medial surfaces of the left hemisphere. *a*, central fissure; *a'*, bottom of central fissure; *b*, intraparietal sulcus; *c*, postcentral sulcus; *d*, rim of hemisphere separating medial and dorsolateral surfaces; *e*, sulcus callosus marginalis; *e'*, bottom of sulcus callosus marginalis. Stippled areas are the posterior bank of central fissure and superior bank of sulcus callosus marginalis. The small figures are of such size that each would cover one square millimeter of cortex if the entire diagram were reduced to actual size. (From Marshall, Woolsey and Bard.)

Rioch[269] found that decorticate cats are able to localize quite accurately the source of a moderately soft scraping, hissing, or clicking sound. Of the special senses audition appears to be the most highly organized at subcortical levels of integration.

The vestibular system apparently projects also to the temporal lobe, for subjective dizziness occurs when this region is stimulated electrically in conscious human subjects. There is also evidence of such a projection to the temporal lobe of lower animals.[124] Nothing, however, is known of the course of the paths which carry impulses from the vestibular portion of the eighth nerve to the cortex.

The Visual Areas.—The visual centers are known with considerable precision. In order to explain the disturbances in vision which result from lesions in the visual centers, a word must be said about the formation of images upon the retina and the course of the afferent fibers which pass from the retina to these centers. The optical mechanism of the eye is such that the image of any object at which one looks is inverted when it falls upon the retina. Consequently the upper part of the visual field falls on the lower part of the retina, the left half of the visual field falls on the right half of the retina, etc. The optic nerves from the two eyes meet at the optic chiasm, and there about half the fibers in each nerve cross to the opposite side of the brain and follow a course which leads to the visual center, which is contralateral to the eye in which they arose. The other half of the fibers in each nerve do not cross in the chiasm, but continue through the brain by a path which leads to the visual center on the same side of the body as the eye in which they arose. The remarkable thing about this arrangement is that the fibers which cross in the chiasm are those which arise from the medial half of both retinas. As a result, the left visual center receives all impulses which arise from the left halves of the retinas of both eyes, and since these impulses are set up by objects whose images are inverted upon the retinas, this visual center is affected by the right half of the visual field. Conversely the right visual center is affected by the left half of the visual field. A consideration of Fig. 74 will make clearer this rather complicated situation. This arrangement is associated with binocular vision, that is, the simultaneous use of both eyes in viewing a single object. In the lower vertebrates, in which the eyes are on opposite sides of the head and consequently have different visual fields, the crossing in the chiasm is complete. In intermediate forms, such as the dog and the cat, something like 80 per cent of the optic nerve fibers cross. The arrangement in man is of obvious importance in causing the images formed by the two eyes to effect simultaneously the same sensory centers in the brain.

Because of this arrangement certain characteristics appear in injuries to the various parts of the optic tracts. A lesion located distal to the chiasm will cause blindness in one eye alone. Lesions, such as those produced by the pressure of a pituitary tumor upon the chiasm, may destroy the function of those fibers which are crossing in the chiasm, and a type of blindness known as *bitemporal hemianopsia* results. This is a loss of sight in the temporal half of both visual fields, occasioned by destruction of the decussating fibers, which, as we have pointed out, arise in the nasal half of each retina. Complete destruction of one of the visual tracts between the chiasm and the sensory area of the cortex produces a condition called *homonymous hemianopsia*, or blindness in the same half of the visual field of both eyes. Thus destruction of this part of the left optic tract which contains fibers from the left half of both eyes will produce blindness for the right half of their visual field. The visual area of the

cortex is located about the calcarine fissure on the median and posterior surfaces of the parietal lobes. Its area is sufficiently great to make it probable that a lesion will involve only certain parts of it, and as a result produce blindness in only part of the visual field. By correlating the position of lesions with the resulting loss of vision Holmes and Lister[293] were able to determine what part of the visual area corresponds with each part of the retina. They found that the center of each retina, or macula, is represented in the posterior part of the visual area. The superior quadrant of each eye is represented in the upper, and the inferior quadrant in the lower half of the visual area anterior to the center for macular vision. It had previously been held that the center of each retina is represented in the visual area of both sides of the brain. This was because in the lesions of civil life homonymous hemianopsia rarely affects the center of the visual field in the blind half of the eyes. Holmes and Lister found, however, in cases where the visual area of one occipital lobe was completely destroyed that vision was lost in the central part of the corresponding half of the retina quite as completely as in the more peripheral portions. They consequently concluded that the macula, like the rest of the retina, is not represented bilaterally in the cortex. The discrepancy in the condition, as they observed it, in wounded soldiers, and as it occurs in civil

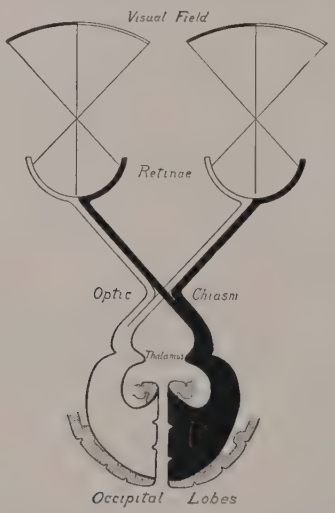


Fig. 74.—Afferent paths connecting the retina with the visual area of the cerebral cortex.

life, depends upon the fact that in the latter case the cause of the lesion is usually a disturbance of the circulation of the cortex as the result of thrombosis, hemorrhage, etc. The macular part of the visual area is supplied with capillaries from two sets of arteries, those of the median and of the lateral surface of the occipital lobe. An occlusion of the median supply would destroy the visual area for the peripheral half of the retina, but would leave intact the macular region which would be sufficiently nourished by the blood from the lateral arteries.

Riddoch[306] has noted that in case of injury to the occipital lobe, dissociations in visual sensations occur which are quite comparable to the dissociations which may occur in lesions of the sensory cortex for cutaneous and deep sensibility. These manifest themselves in the case of patients who are recovering from a functional disturbance of the visual areas. The first visual perception to appear is the recognition of the *movement* of an object in the visual field, which occurs long before the object *as such* can be recognized. A case is also described in which vision persisted in one half of the visual field on recovery from an occipital injury, and yet things which were seen quite well could not be oriented in space, and thickness and depth found no place in the visual perception.

The sensory areas of the cortex and thalamus are the end points to which we trace the afferent impulses which give rise to sensation. We are not justified, however, in concluding from this that they are the regions in which the phenomena of sensation and consciousness occur. Rather should they be thought of as important junction points on the afferent side of the complex network of neurons which link up the various centers of the cerebrum and in which are carried out our mental processes, which give rise to consciousness. In a similar way the motor centers which we are to consider in the next chapter are the junction points from which efferent impulses for movement leave the cortex.

CHAPTER XIX

THE MOTOR FUNCTIONS OF THE CEREBRAL CORTEX AND BASAL GANGLIA

It has already been pointed out (Chapter XI) that after removal of the entire cerebral cortex certain mammals, such as the cat and dog, are still able to carry out complex motor responses of a very perfect nature. Such animals are able to right themselves, have good equilibrium, walk and run, are capable of displaying anger and fear, swim when thrown in the water, eat if food is brought in contact with their mouths, and reject food of disagreeable taste. Many of the reactions of such animals are predictable because they show scarcely any signs of being influenced by past experience. The decorticate dog shows no sign of recognition of its master or of other animals, it does not recognize food as good to eat by its mere appearance nor does it display any other evidence of acquired modes of behavior. The mechanism by which the retention and association of the effects of past experience modifies behavior evidently resides in the complicated meshwork of neurons which compose and connect the various parts of the cerebral cortex. We shall see later in considering the formation of conditioned reflexes how previous experience may alter the nature of even involuntary responses to simple stimuli. In the present place it will suffice to point out that unless we have considerable knowledge of the past experience of an animal it is impossible to predict how it will respond to certain situations. Responses of this type consequently are not obviously and invariably related to any particular stimulus as are the simpler reflex responses and consequently appear to arise spontaneously in the nervous system. They are consequently called *voluntary acts* which we shall take to imply that their nature and occurrence is related quite as closely to preexisting conditions in the nervous system as to the immediate situation which brings them forth. It would, however, be incorrect to assume that the cerebral cortex is concerned only with the elaboration of acquired modes of behavior. As we have seen, it has much to do with postural reactions and the regulation of muscle tone. These are functions, which as every bit of valid evidence indicates, are not acquired, but emerge quite independently of the animal's experience.

Situated beneath the cerebral cortex is a part of the forebrain which is of more ancient lineage. This is the group of nuclear masses known as the basal ganglia. Their functions appear to be chiefly motor. It is a curious fact that the behavior and reactions of decorticate cats and dogs in which these structures have been removed are essentially the same as those of animals which lack only the cortex.[269] This fact suggests that the main influences of the basal ganglia are exerted upon activities of cortical origin. Because of this the little that is known of their functions will be presented after considering the cortical motor functions.

THE MOTOR AREAS OF THE CEREBRAL CORTEX

Just as we saw in the last chapter that there were certain junction points, or sensory areas, by which afferent impulses are led into the cerebral cortex so

there are certain foci from which efferent impulses leave the cortex to initiate movement in the skeletal muscles. These are the *motor areas* of the cortex. Their situation and the muscles or groups of muscles related to each part of the motor area have been made out by two methods. In animals, and, under exceptional conditions, in man, the cortex may be excited locally, preferably by some method of unipolar electrical stimulation, and the muscles brought into action may then be noted. Conversely, parts of the cortex may be removed and the distribution of the muscles which are then no longer under this control may be determined.

The Motor Cortex (Area 4 of Brodmann) and the Pyramidal System.—By means of the two experimental methods just mentioned it has been found that the cortical zone known as area 4 of Brodmann (area gigantopyramidalis) is a functionally important motor region. It contains at least the majority of the cell bodies whose axons make up the pyramidal tract and innervate directly the motor neurons of the cranial and spinal nerves. Although it is not the only motor projection area of the cortex, it was the first to be so designated, and for that reason it is usually called, without any qualification, the motor cortex. In the brains of primates this area lies immediately in front of and extends into the central sulcus or fissure of Rolando (Fig. 70). In the dog and cat it borders the cruciate sulcus, which lies near the frontal pole of the hemisphere, and apparently occupies a region homologous to the precentral gyrus of the primate brain.

The motor cortex as defined above possesses a characteristic structure. It contains in its fifth layer (sometimes called the fourth because here the internal granular layer is so thin as to be negligible) the Betz cells, a type of large or giant pyramidal cells, not found elsewhere in the cortex. That the axons of these cells form the pyramidal tract is suggested by the complete degeneration of the latter which follows removal of this cortical field. But no surgical ablation can possibly be confined strictly to the cortex containing Betz cells. The point is therefore somewhat more conclusively settled by the observation that these cells undergo chromatolysis when the pyramidal tracts are cut. Evidence that the reactions elicited by electrical stimulation of the motor cortex are due to the direct excitation of the large pyramidal cells of the fifth layer has been put forward by Dusser de Barenne.[282] Employing a method of thermocoagulation and determining the extent of the lesions by histological studies, he has been able to show that after complete destruction of the outer three (or four) layers of the motor cortex of monkeys the threshold and character of the responses to direct electrical stimulation are unchanged. Several considerations indicate that the reactions obtained are due to direct excitation of the bodies of the large and giant pyramidal cells.

Some confusion exists concerning the proper definition of the term "motor cortex." A delimitation founded entirely on histological features is meaningless unless it can be shown that the structural differentiation has some functional correlate. On the other hand, a purely physiological definition, based entirely on the nature of the results of stimulation, is not much more satisfactory. The history of physiological progress shows that until a function is recognized as the peculiar correlate of some fairly definite structure, it is apt to defy any sort of precise analysis. Thus while one can agree with Walshe's objection[315] to the statement that "the limits of the motor area are determined by its cellular structure and not by its electrical excitability," it is not easy to perceive the advantage of his claim that the term "is a physiological one and cannot be used to indicate either the precentral area, or that part of it known as the area gigantopyramidalis." Now the classical motor area of the physiologist has for years been defined as that cortical region from which highly *discrete* movements can be elicited by direct electrical stimulation, and there has accumulated much good evidence favoring the view that this area is coextensive with area 4 of Brodmann. The fact that other areas of the cortex yield movement on stimulation has stood in the way of acceptance of this correlation. Chief among these areas is that numbered 6 by Brodmann; it lies immediately in front of area 4 and differs from it histologically only by the absence of Betz cells. The movements produced by its stimulation can be divided into two specific types of somatic reactions:[273, 285] (1) Responses of individual muscles which are mediated through area 4,

but which are never quite so discrete as those from area 4; and (2) complex stereotyped movements involving a whole limb or some other large division of the body, which depend on extrapyramidal connections. In view of these facts it seems clear that the area gigantopyramidalis is specifically concerned with the mediation of a certain type of movement. Very recently the distinction between areas 4 and 6 has been made particularly sharp by Hines[292] in stimulation experiments on the precentral cortex of monkeys. She has found that if a line be drawn through the most anteriorly situated points from which isolated limb movements can be elicited by a threshold stimulus, "pieces of cortex removed from an individual brain anterior to this line will show themselves by examination of serial sections to contain cortical lamina characteristic of Brodmann's area 6 and those posterior, of Brodmann's area 4." Nevertheless, as Hines points out, there are so many individual differences that it is impossible to draw on a cortical diagram a line representing for all members of the species the boundary between areas 4 and 6.

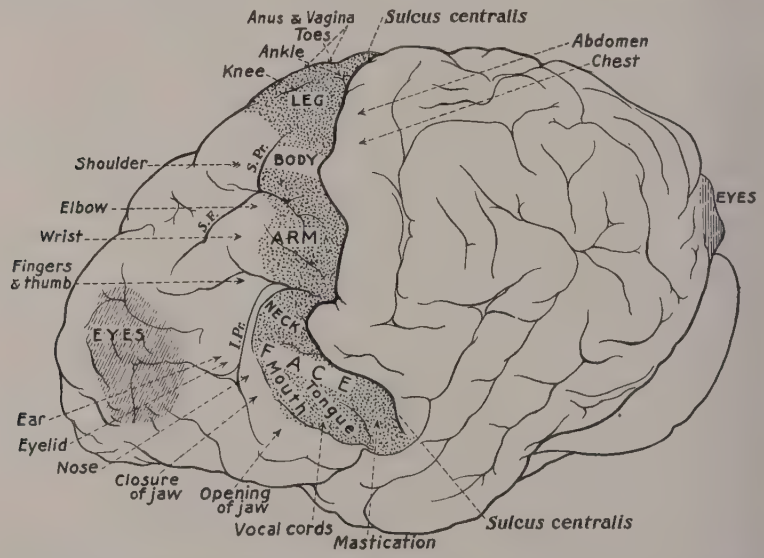


Fig. 75.—Outer aspects of the brain of the chimpanzee, showing the position of the motor cortex. Electric stimulation at the parts indicated causes movements of the corresponding muscle groups. (After Sherrington.)

When the motor cortex is explored with stimulating electrodes, it is found that definite parts of the musculature of the opposite half of the body are thrown into action by the stimulation of definite parts of the area. There is then, just as in the case of the somatic sensory area, a region corresponding to each anatomical part of the body. In the carnivores, head, foreleg, and hindleg motor zones can be distinguished, but only a relatively small number of movements of each of the parts can be elicited by localized stimulation. In the monkey the area is larger than in the lower mammals, it is more sharply subdivided into distinct parts, and its stimulation yields more finely graded responses. In this higher form it is possible to obtain by punctate stimulation movements which are isolated, for example, extension of the thumb without any other movement in the extremity. Exploration of the human cortex with stimulating electrodes has shown that with the further development of the primate hemisphere the subdivision of the motor area has progressed to an even greater

extent. Foerster,[285] in his stimulation experiments on human subjects, was able to show that area 4 contains separate representations not only for single muscle groups but also for single muscles.

In the primate cortex with its well-marked central sulcus (fissure of Rolando) the movements of the muscles of the head are occasioned by excitation of the lower portion of the precentral gyrus; above it the neck, arms, trunk, and legs are represented in turn (Fig. 75). In the monkeys and anthropoid apes the motor area lies in the anterior wall of the central sulcus and extends over a large part of the outer surface of the precentral convolution; in man the gigantopyramidal area is largely confined to that part of the convolution which borders the sulcus; i.e., it is buried beneath the outer surface of the cortex.

Removal of the motor cortex, which as we have seen is also part of the sensory area, produces certain motor deficiencies. In the cat and dog these are relatively slight. There is no paralysis of locomotion, the only definite motor defects being a permanent loss of the placing reactions and a profound deficiency of the hopping reactions (see page 142). After unilateral removal of the motor cortex, these defects are limited to the limbs of the opposite half of the body. When area 4 is removed from the brain of a monkey the resulting defects are more pronounced. At first there is a profound contralateral paralysis which is accompanied by a state of flaccidity of the muscles. Then in the course of a few days motility reappears, first in the proximal joints, later in the more distal joints of the limb. Slowest to reappear are the movements of the fingers and toes, and for a long time they are clumsy and ataxic. Long after the movements of the proximal joints have become quite normal the animal is still unable to employ the fingers in fine movements, such as picking up small objects. Eventually, however, the degree of recovery is very great, but it is usually possible to detect some impairment in the action of the fingers of the affected limb. When only the motor representation of one part of the opposite half of the body is removed that part shows the same motor deficiencies that are produced in it by ablation of the entire motor area.

In the higher primates the motor impairment which follows removal of the motor cortex or one of its subdivisions is more profound and longer lasting. Fulton and Keller,[288] paying special attention to the appearance of abnormal reflexes, found that after extirpation of the leg area of one cortex in the chimpanzee, the opposite hind extremity exhibits absolute areflexia during the first twenty-four to thirty hours. The depression of reflexes is similar to that seen in spinal shock (page 87). After from two to four days the hip shows some return of "voluntary" power, the knee after four days, the ankle not before twenty-five days, and the toes after from forty to sixty days. In man the impairment in motility brought on by lesions of the motor area is more profound and of longer duration, but recovery may be very considerable.

Effects of Pyramidal Section.—Owing to the fact that a cortical ablation cannot possibly remove only the cells which give rise to the pyramidal tract, the method of choice for studying the effects of withdrawal of pyramidal impulses from spinal mechanisms is to sever one or both of these corticospinal tracts below its origin. This can be done in isolation by cutting the medullary pyramids at the level of the trapezoid body. Studies by Tower[178, 311, 312] in which this procedure was used have revealed several facts of importance which cannot be made out with any assurance by cortical ablation or by stimulation

of the cortex when all descending systems are intact. The functional deficits thus produced can be attributed to loss of pyramidal influence, while the motor activities of cortical origin which can still be evoked are attributable to the extrapyramidal systems of the cortex. The latter will be discussed in the following section.

In experiments on cats Tower[178] found that the functional deficit produced by pyramid section is expressed in three ways: (1) loss or impairment of specific responses such as the placing and hopping reactions to an extent comparable to that which follows decortication, (2) impairment of phasic movements such as pawing and clawing, and (3) a raised threshold of spinal flexor activities. According to Tower, extensor mechanisms in the cat are not appreciably affected by removal of pyramidal influence.

The results of a similar study carried out by Tower[312] on monkeys are of great interest. She states that "The most conspicuous result of unilateral pyramidal lesion in the monkey is diminished general usage and loss of initiative in the opposite extremities. The loss of initiative is grave, but not complete. When both sides are free to act, initiative of almost every sort is delegated to the normal side, but if the normal side is restrained the affected side can, with sufficiently strong excitation, be brought to act." The affected side engages in stereotyped activities such as progression, climbing, and gross righting. The least stereotyped motor acts are gravely affected: "Thus all discrete usage of the digits disappears, together with the corrective movements for unusual postures, and the ability to take accurate aim." The ability to grasp and to release a grasp is curtailed. The threshold of spinal reflexes and the tone of the musculature on the affected (opposite) side is diminished. The positive supporting reaction, incorporating both flexors and extensors, is depressed. The hypotonia, like that of the decerebellate primate, is accompanied by slow, full tendon reflexes. Deficit in phasic movements is conspicuous and this, like the hypotonia, is the result of lowered excitability of the spinal motor mechanisms. After bilateral pyramidal lesion the effects of unilateral section are duplicated, but now the animal can make use only of residual extrapyramidal capacities to compensate the defect; it can no longer rely on one normally innervated side for compensation. Hypotonia of the axial musculature is added to that of the proximal portions of the limbs; the head totters, the body sags from its points of support and the abdomen bulges. Improvement extends over several weeks; first sitting, then standing and finally locomotion return, but each of these activities is accomplished with difficulty and entered into with reluctance. One of the most significant conclusions to be drawn from these experiments is that elimination of the pyramidal system does not result in symptoms of release. It produces a disorder which may be called "hypotonic paresis." Further, Tower's studies show clearly that voluntary action by no means depends entirely on this system. It is doubtless extremely unlikely that a cortical or a subcortical lesion in man would ever give a deficit that was purely pyramidal. Tower points out that the one reliable sign of involvement of the pyramidal system by a cortical lesion is a defect in the minute control of the skeletal musculature. Other results of clinically occurring cortical lesions, particularly spasticity, are due to interference with extrapyramidal innervations.

Other Motor Areas of the Cortex: The Cortical Extrapyramidal Systems.—As we have seen the motor cortex is that region which is characterized by the

presence of Betz cells and from which discrete individual movements can be obtained by electrical stimulation of the neurons whose fibers make up the pyramidal tracts. It is not, however, the only electrically excitable area. Foerster, for example, speaks of several motor areas, the pyramidal and extrapyramidal (Fig. 70). He has shown in stimulation experiments on the human cortex that isolated motor effects similar to those obtained by stimulation of area 4 may be obtained from the cortex of the summit of the precentral gyrus (area 6 a alpha), and from the postcentral gyrus (areas 3, 1, and 2). Such effects are dependent on the intracortical connections of these areas with area 4, which is the area for isolated innervations. When area 4 or the pyramidal tract has been destroyed, stimulation of areas 6 a alpha, 3, 1, and 2 produces complex movements of rotation of the eyes, head, and trunk to the opposite side and of flexion or extension of the contralateral limbs. These so-called adversive movements are also obtained, independently of area 4 and the pyramidal tract, from other parts of the human cortex. They are evoked by strong stimulation of area 6 a beta, which occupies the posterior part of the superior frontal convolution, of areas 5 a and 5 b located in the superior parietal lobule and of area 22 which is situated over the posterior part of the superior temporal convolution. Bucy[273] has shown that the *premotor area* of the monkey brain possesses a similar electrical excitability. This region (area 6 of Brodmann) lies immediately rostral to the motor area. Its stimulation yields two sorts of movements in the opposite half of the body: (a) discrete motor responses which depend on the integrity of area 4 and the pyramidal tract, and (b) adversive movements or complex reactions of a limb mediated by descending fibers which are independent of the pyramidal tracts, for the typical responses are evocable after complete ablation of area 4. In addition it was found that movements of the ipsilateral lower limb can be evoked by stimulation of the superior lip of the precentral sulcus, i.e., at a point in the posterior upper part of area 6.

Richter and Hines[300] have shown that extirpation of the upper part of area 6 produces contralateral forced grasping, a condition in which strong flexion of the digits occurs whenever an object is placed in the hand. This response is sufficiently strong to support the animal's entire weight when it is made to hang from a bar. The symptom is transient unless the extirpation is bilateral, a fact indicating some degree of ipsilateral innervation from this part of the cortex. According to Hines[292] forced grasping is the only definite symptom which invariably follows cortical extirpations in the monkey which are limited to area 6. It appears that this area contains projection systems for the inhibition of flexor activity; grasping follows its removal. The extrapyramidal nature of the system is demonstrated by the fact that pyramid section does not produce grasping of this type. Further, stimulation of area 6 in an animal with the corresponding pyramid cut causes inhibition of flexor activity.

There is also evidence that the premotor area is concerned with the integration of complex volitional movements.[287] Even when area 4 is removed from both cortices of a monkey or chimpanzee, the motor recovery is considerable. That this is probably largely due to the functioning of the premotor area is indicated by the fact that when areas 4 and 6 are removed from both sides, the animal is totally incapacitated, at least for a long period of time. Bucy and Fulton[274] have shown that when removal of areas 4 and 6 from one hemisphere is combined with extirpation of either area 4 or 6 from the other, the animal re-

mains capable of some degree of integrated movement in all four extremities. Thus the ablation experiments furnish further evidence in favor of an ipsilateral innervation from the primate cortex.

The experiments of Tower on monkeys (see above) in which one or both pyramids were sectioned give a clear picture of the extent of extrapyramidal action. When one compares the very considerable motor capacities of these preparations with the grave paresis and muscle hypertonia of animals subjected to removal of areas 4 and 6, the contribution of extrapyramidal influence to regulation of movement and tone becomes forcefully apparent. The types of movement which can be induced by cortical stimulation in cats after section of both pyramids have also been carefully recorded by Tower.[311] They are slow to appear, build up slowly, and tend to outlast the stimulus. Evoked under light anesthesia, they may attain the shape of integrated and significant acts, often rhythmic in character and involving the assumption of postures. They contrast sharply with the simple phasic crossed movements appearing without delay which are induced by stimulation of the pyramidal tract. There are in the cat's cortex four regions from which these extrapyramidal actions can be provoked: two are on the frontal pole, one is in the parietal region and another lies at the caudal or occipital pole of the cortex.

The lack of symptoms of release after pyramidal section suggests that the inhibitory function of the cerebral cortex on spinal motor mechanisms is exerted chiefly over extrapyramidal pathways. Experiments in which the responses to electrical stimulation of the cat's cortex were compared before and after pyramidal section showed that the inhibitory function is indeed predominantly an extrapyramidal one (Tower[311]). It is exerted on movement as well as on tone. The cortical mechanisms inhibiting movement are distributed widely over the cortex, while relaxation of tonic contraction (e.g., the pseudodecerebrate rigidity of light ether anesthesia) can be evoked from areas which are restricted and correspond rather closely to the motor areas. The peculiar feature of the inhibitory action exerted through extrapyramidal systems is that the muscular relaxation may not be accompanied by any motor action. Pyramidal discharge, on the other hand, will involve relaxation of antagonist muscles through reciprocal inhibition, but this is invariably coexistent with active contraction in the agonist.

The extrapyramidal projection fibers of the cortex apparently end in the various motor nuclei of the brain stem from which impulses are relayed by a series of neurons to the spinal motor outflow to muscle. Very little is known of the neural connections of the extrapyramidal systems. The subcortical structures chiefly concerned are the basal ganglia, the red nuclei and the substantia nigra. These are considered in the final section of this chapter.

Spasticity and Other Phenomena of Release.—In the cat and dog removal of the frontal pole of the cortex (Fig. 56) not only produces in the contralateral legs motor defects, but permits the development of a marked extensor hypertonia whenever the legs are freed from the duty of supporting the body and are not engaged in any phasic activity.[179, 269] In these carnivores it is quite impossible, because of juxtaposition and overlapping of cortical areas, to remove even a part of the true motor cortex (area 4) without at the same time extirpating tissue belonging, both functionally and anatomically, to another area. This is shown when one compares in the cat the results of frontal pole removal with section of the pyramid at the level of the trapezoid body. Tower[178]

found that while pyramid section in the cat results in typical motor defects (e.g., loss of placing and deficiency of hopping reactions) it does not produce any marked rigidity. The latter, however, follows the subsequent ablation of the frontal pole.

In primates, from monkey to man, any *extensive* ablation of precentral cortex or interruption of descending projection pathways leads to a similar dual effect. The deficiency phenomena, consisting chiefly in impairment of all skilled and isolated movements, are combined with release phenomena, usually described by the rather vague clinical term "spasticity." These release phenomena are: muscle hypertonia (flexor in arm, extensor in leg), clonus, and augmentation of tendon reflexes. The question whether motor paralysis and the release phenomena are produced by interference with a single or with two distinct cortical mechanisms was under intense discussion for some years. On the one hand, Fulton and his collaborators[287, 297] have contended, as a result of extensive ablation experiments on a variety of infrahuman primates, that motor paralysis and flaccidity characterize lesions of area 4, while spasticity and the associated increase of tendon reflexes is the distinctive manifestation of a premotor (area 6) loss. This view was subjected by Walshe[315] to a critical analysis in which the impressions of the English school of clinical neurologists are summated with certain alleged imperfections of Fulton's interpretations to arrive at the conclusion that there is no basis for distinguishing between separate "motor" and "premotor" syndromes. The only symptom which Walshe can attribute to lesions of the premotor cortex is forced grasping. The problem seems to have been solved, at least in its major aspects, by some observations of Hines,[292] and in a manner which shows that Fulton's thesis is correct in its general, if not in its detailed, reference to cortical topography. The experiments carried out by Hines on the monkey (Macaca mulatta) show that persistent symptoms of "spasticity" with a minimum of residual paralysis can be produced by a simple ablation of a slender strip of tissue, about 3 mm. in width, in the anterior part of the true motor cortex (area 4). Since section of the pyramids does not cause this release phenomenon, it may be concluded that the "strip" region, now designated area 4-S exerts its effects through an extrapyramidal pathway. When only the part of area 4 lying posterior to the "strip" is removed a rather transient paralysis supervenes, but phenomena of release do not apparently appear; at least in Hines' experiments they "were difficult to demonstrate." The distribution of paralysis which follows lesions of the motor cortex and the discrete movements which are evoked by its stimulation demonstrate a topographical sequence of the controlling motor elements. No such localization is evident in the inhibitory mechanism revealed by removal of the "strip" area. A partial ablation here produces transient effects in both contralateral limbs. We may conclude then that area 4, the motor cortex of the physiologist, contains two functionally separate neural mechanisms: one, anatomically distributed over the entire area, mediates discrete movements through the pyramidal tracts; the other, seated anteriorly in the area, has as its chief function the inhibition of muscle tone through extrapyramidal pathways. Spasticity is accordingly a sign of release of lower mechanisms from cortical inhibition exerted extrapyramidally.

Jacksonian Epilepsy.—When the strength of the stimulus applied locally to the motor cortex of an animal is great, its influence spreads so that adjoining motor cells are brought into activity and larger and larger groups of muscles take part in the response. This pro-

gressive "march" of the response to cortical stimulation is usually limited in its spread to the opposite half of the body. Very similar results are obtained in man when the motor area is the site of some form of irritative lesion, such as that produced by an expanding meningeal tumor, a spicule of bone or a scar of traumatic origin. Such stimulation causes contraction in the corresponding muscular area; the contraction then spreads to neighboring groups of muscles and may involve the entire opposite side or even the entire body. When the irritative source of the attack lies in the premotor region of the frontal lobe (area 6) the seizure commences, as might be expected on the basis of stimulation experiments, not in a single muscle or small muscle group, but with complex movements affecting an entire extremity or with turning of the head and trunk. Ordinarily those attacks which arise from the motor areas of the frontal lobe (motor and premotor areas) are not accompanied by any special subjective sensory phenomena. When, however, the seizure has its origin in the postcentral extrapyramidal region, it characteristically begins with some definite sensory impression (aura). Thus an understanding of the topography and specific responses of the different excitable cortical areas is essential for the surgeon who would attempt to attack this disease by removing its source.

The Results of Injuries to the Efferent Pathways from the Cortex.—The arrangement of the pyramidal fibers in their descent from the cortex imposes certain characteristics on the distribution of the paralysis which results from lesions in different parts of their course. Since lesions of the human cortex rarely result in a complete destruction of the motor area, the resulting paralysis is usually limited to one limb or to a few groups of muscles on the opposite side of the body. Such a limited, unilateral paralysis is called *monoplegia.* In the deeper parts of the brain the pyramidal fibers converge with the result that a lesion the size of a pea in the internal capsule will produce complete destruction of the tract. Monoplegia is consequently a rare result of lesions at a capsular level, the paralysis usually involving the entire opposite half of the body. Such a condition is known as *hemiplegia.* Lesions in the brain stem as far back as the pons will similarly produce complete contralateral hemiplegia. At the pons the first group of pyramidal fibers cross to the opposite side to connect with the motor neurons of the facial nerve. Lesions in the lower part of the pons consequently do not involve these fibers, and the facial muscles of the opposite side do not share in the paralysis. A lesion at this level, however, will interrupt the tracts from the opposite cortex which have crossed to join the facial nucleus on the side of the lesion. Consequently the face becomes paralyzed on the same side as the lesion. The decussation of fibers to the hypoglossal nerve produces a similar alternating paralysis of the muscles of the tongue and of the limbs in the case of lesions in the medulla. The tongue is paralyzed on the same side as the lesion, the arm and leg on the opposite side, while the facial muscles of both sides escape. Such a condition is rare, however. Unilateral lesions below the decussation of the pyramids cause paralysis which may affect those muscles whose motor neurons lie below the level of the lesion and on the same side of the body.

When a hemiplegia is produced by a lesion within the internal capsule (hemorrhage in this region being the most common cause of hemiplegia), the ensuing voluntary paralysis in the arm and leg of the opposite side is usually accompanied by some degree of hypertonia, which on the basis on the work of Fulton of Hines and of Tower may be attributed to interruption of extrapyramidal pathways. This condition in man is not unlike decerebrate rigidity in the cat and dog, which, as we have seen (Chapter XIV), is largely the result of removal of a cortical influence. There is, however, one significant difference between the two conditions. In the carnivores the rigidity is extensor in upper and lower limbs whereas the hemiplegic patient typically presents a rigidity which is flexor in the arm, extensor in the leg. Extensor rigidity in the leg can readily be interpreted as a sign of overactivity in an antigravity mechanism, and thus it may be correlated with decerebrate rigidity, but the hypertonia of the arm flexors cannot be so readily explained. Walshe[314] has suggested that the semiflexed position of the arm represents the result of release of a prehensile function which, in the course of evolution, has developed in connection with the assumption of an erect bipedal posture. But Brain has pointed out that prehension in man is under pyramidal management and would therefore scarcely be released by a pyramidal deficiency. It is perhaps significant that the posture of the arm in hemiplegia is identical with the resting position of the forelimbs of monkeys and anthropoid apes. When these primates walk or run on all fours, the prehensile upper limbs become locomotor props and the predominant tonus becomes necessarily extensor. Proceeding on the hint given by this fact, Brain[271] found that if a hemiplegic person takes the quadrupedal attitude the affected arm assumes an extended posture and shows

such marked rigidity of the extensors of the elbow that this joint cannot be passively flexed. When the patient resumes the erect position, the arm resumes the attitude of semiflexion at the elbow. On the basis of this fact Brain has suggested that as decerebrate rigidity in cats and dogs is reflex quadrupedal standing, so the hemiplegic posture in man is reflex erect standing, which represents a reversion to a stage of evolution between the anthropoid ape and man.

Paraplegia is the term used to describe paralysis confined to the lower limbs. It may be produced in man as a result of a bilateral lesion of the medially situated leg areas of the motor cortex, but such cerebral paraplegias are not common. When they do occur the legs usually exhibit an extensor hypertonia similar to that which is characteristic of hemiplegia of capsular origin. This condition, spoken of as *paraplegia-in-extension*, is most frequently the result of a bilateral cord lesion which involves one group of descending fibers (presumably extrapyramidal) to the leg spinal segments but spares other descending tracts. If the lesion functionally divides the greater part of the cord or if there has been an actual transection, the condition is that which has already been described in discussing spinal shock and recovery from spinal shock in man (page 88). Some degree of flexor withdrawal of the leg can be reflexly obtained unless the cord has been extensively affected. At first it can be evoked only by nocuous stimulation of the foot, and it then consists of little more than movements of the toes. Later, with the appearance of the mass reflex, strong flexion at hip and knee occurs in response to slight stimulations of any part of the leg. Extensor responses are absent or minimal, a knee jerk usually being the only evidence of extensor activity. Furthermore the extensor muscles exhibit hypotonia while the flexors tend to be hypertonic. The condition is therefore spoken of as *paraplegia-in-flexion*.

Paraplegia-in-flexion may be regarded as the result of complete isolation of the spinal motor control of the legs from all cerebral influences. The predominance of flexor activity and flexor tone is an expression of the isolated activity of a spinal mechanism. When, as in hemiplegia or paraplegia-in-extension, the lesion has interrupted only certain descending impulses of cortical origin, voluntary paralysis is accompanied by overactivity of other descending systems. It is commonly believed that the extensor rigidity observed in these cases is symptomatic of interruption of the pyramidal tracts, but, as we have seen, there is evidence that the condition results from removal of some extrapyramidal cortical influence.

MOTOR FUNCTIONS OF THE BASAL GANGLIA

Comparative anatomical studies show that the so-called basal ganglia make up the most primitive part of the forebrain. The phylogenetic precursor of the mammalian striatum and pallidum is well developed in lower vertebrates which lack a cortex. The basal ganglia are highly developed in reptiles and birds which have poorly developed cortices, and in these forms they appear to be of relatively greater importance. In the higher mammals this portion of the forebrain is overshadowed by the cortex, and shows a development of its dorsal part and a reorganization of structure which are evidently related to the enlargement of the cortex.

Anatomical Aspects of the Basal Ganglia.—The physiologist finds it necessary to rely heavily upon the anatomical features of the basal ganglia in order to supplement the scant knowledge gained from experimental analyses of these structures by inference from their connections. They are made up of two main parts: the *caudate nucleus and putamen* (the striatum) and the *globus pallidus* (the pallidum). The putamen and globus pallidus are often designated the lenticular nuclei, but since the putamen and caudate appear to be, in general, phylogenetically newer structures (neostriatum) than the globus pallidus (paleostriatum) this grouping is not particularly appropriate. Because they are connected with the basal ganglia and probably represent portions of the same functional system, the subthalamic body, the red nucleus and the substantia nigra, all belonging to the mesencephalon, and various diencephalic nuclei are often included in this complex. The claustrum and amygdala, which are masses

of gray matter lying close to the putamen and tail of the caudate, respectively, are usually regarded as parts of the basal ganglia.

The globus pallidus, which consists entirely of large cells of the motor type, is the chief efferent mechanism for the striatum (caudate and putamen) from which it receives its main afferent supply. There is evidence, however, that some fibers descend directly from the striatum to the substantia nigra (Rundles and Papez). The principal motor projection of the basal ganglia is the *ansa lenticularis* which distributes fibers to many parts of the brain: thalamus, hypothalamus, zona incerta, subthalamic body, red nucleus, substantia nigra and reticular substance of the mesencephalon (for details see Fulton[124] and Rioch[307]).

The chief afferent connection of the striatum is made up of fibers of cortical origin, some of which, according to Cajal, are collaterals of fibers in the internal capsule. The cortical projections are from the extrapyramidal areas and terminate in the caudate nucleus and putamen. The caudate nucleus also receives fibers from the midline nuclei of the thalamus and perhaps from other thalamic nuclei.

For various reasons the details of the connections of the basal ganglia are not easy to make out. Those which have been mentioned should be regarded merely as the ones generally agreed upon. A point of very real significance has been emphasized by Fulton,[124] namely, that designating the descending projections of the basal ganglia, more particularly the ansa lenticularis, as the principal extrapyramidal descending system should not be taken to mean that the extrapyramidal system is subcortical. As we have already seen, the extrapyramidal functions of the cerebral cortex are as conspicuous as the pyramidal, and there is evidence that they are mediated through direct connections with almost every subcortical motor center. It is also possible that some of the corticothalamic fibers represent pathways over which extrapyramidal cortical influences are brought to bear on the motor mechanisms of the brain stem.

Functional Analyses of the Basal Ganglia.—Physiological exploration of these structures has yielded surprisingly little information. No other major subdivision of the brain has proved so refractory to experimental analysis.

Evidence From Animal Experiments.—A comparison of the activities of animals (cats and guinea pigs) in which the neocortex was removed with those of others in which the paleocortex, striatum and pallidum were also ablated has failed to suggest the nature of the functions of the basal ganglia.[269, 307] The results, however, do tell us that *in the absence of the cerebral cortex* the striatum and pallidum play no fundamental role in the fashioning or execution of the following modes of behavior: locomotion; postural adjustments such as the hopping, placing, and righting reactions; sleeping; expressions of anger and fear; estrous behavior in the female; and temperature control (Rioch[307]). On the basis of this type of experiment no definite function can be assigned the basal ganglia which is independent of cortical action. Nevertheless, it has been shown that in the absence of neocortex and after degeneration of all corticofugal fibers, inhibition of movement and tone can be obtained in cats by stimulation of the head of the caudate nucleus (Rioch and Brenner[308]).

Stimulation of the basal ganglia in the intact brain of animals or in animals with overlying cortex freshly removed has been carried out by many investigators. Some of the positive results obtained have doubtless been due to

spread of current to neighboring nuclei and fiber tracts. In monkeys Kinnier Wilson carefully explored the putamen and globus pallidus with small needle electrodes inserted through the cortex. He found these nuclei completely inexcitable. In their studies of the hypothalamus (see Chapter XVII) Ranson and his co-workers had occasion to stimulate parts of the pallidum and striatum, but invariably failed to obtain any changes in striated muscle. On the whole, stimulation of these nuclear masses *alone* has given consistently negative results. But proceeding on the theory that the basal ganglia act to condition motor activities which originate elsewhere, Mettler, Lipman, Ades and Culler[303] have recently secured definite effects by the stimulation technique. They showed that electrical excitation of the caudate, putamen or claustrum in cats inhibits phasic movements induced by cortical stimulation, a result reminiscent of the inhibition of movement obtained by Tower on stimulation of extrapyramidal mechanisms in the cortex. Stimulation of the globus pallidus alone was found to be entirely without motor effect, but its excitation during a cortically induced phasic movement inhibited this reaction by converting it into a state of plastic tone: "Thus if flexion of the forepaws was in progress and the globus pallidus was stimulated, a 'holding' effect was observed, in which the limb was held somewhere between the extremes of the phasic flexion. This fixation possessed no element of rigidity or tremor but was curiously plastic—its position could be extensively altered and it would be held equally well in the altered position." All these effects were most marked on movements evoked from the ipsilateral cortex. The inhibiting effects of stimulation of the caudate appear to be exerted on movements of subcortical origin as well as on those of cortical origin, for Rioch and Brenner, as indicated above, obtained them in chronically decorticate animals.

The existence of an intimate functional interrelationship of cortex, caudate nucleus and the relay nuclei of the thalamus has been beautifully demonstrated by Dusser de Barenne and McCulloch.[283] Using the method of local strychninization of the cortex described in Chapter XVIII and recording the more or less continuous electrical changes of the cortex (page 238), they discovered that application of strychnine to the anterior portion of area 4, designated 4-s (the strip area of Hines), has the unique effect of depressing the electrical activity of the rest of area 4. On tracing the pathway over which this influence is exerted they were able to show that it is not intracortical, but that the stimulation of 4-s excites the caudal part of the head of the caudate nucleus which in turn inhibits or suppresses the thalamocortical discharges on which depends the electrical activity of area 4. This physiological analysis confirms the anatomical evidence of a corticocaudate projection and demonstrates a previously unknown field of action of a cortical extrapyramidal system.

The placing of lesions in the basal ganglia of experimental animals is a method which has not yielded any very significant results. Many of the disorders thus produced can be attributed to damage of the rhinencephalon, internal capsule or other neighboring regions.

Evidence From Clinical Disorders.—In contrast to the relatively meager and undramatic results of experimental investigations of the basal ganglia, clinico-pathological studies of these structures are replete with positive suggestions as to their functions. This body of knowledge and opinion is based on the rather crude experiments which nature, through the agency of patho-

logical processes, sometimes performs on this part of the human brain. It is a subject belonging in the province of neuropathology and cannot be given more than the briefest consideration here.

The clinically recognized syndromes of the basal ganglia are of two main types: (1) a condition (Parkinsonism) characterized by resting tremor and more or less rigidity, and (2) involuntary movements (athetosis and chorea). In the disease first described by James Parkinson, and since usually called "Parkinsonism," a rhythmical tremor develops which occurs during rest and usually disappears during a voluntary movement. These features differentiate it from the intention tremor of cerebellar deficit. The Parkinsonian tremor may at first be localized, but as the disease progresses it spreads to the greater part of the striated musculature. Some degree of rigidity is usually associated with the tremor. This hypertonia is peculiar in that it involves both flexors and extensors, thus differing from the spasticity of cortical damage and from decerebrate rigidity. Parkinsonian tremor is usually attributed to lesions in the striatum, pallidum and substantia nigra and there are reasons for supposing that the mechanisms responsible for it are different from those which bring forth the rigidity.[307] The tremor seems to depend on the integrity of the pyramidal system, for it disappears in cases which develop a hemiplegia.

Athetosis and chorea are disorders entirely different from Parkinsonism. Athetoid movements are slow and twisting; they commonly involve the hand or foot, sometimes the entire extremity. Choreiform movements are lightning-quick and involve physiologically unrelated parts. Both of these forms of involuntary action have been attributed to lesions in the basal ganglia, athetosis to pathological changes in the globus pallidus, chorea to lesions in the caudate. But in both conditions other parts of the subcortical extrapyramidal mechanisms, such as the red nucleus and substantia nigra, also seem to be involved in the pathological process.

When one compares the clinical disorders attributable to disease of the striatum and pallidum with the results of animal experimentation directed toward an analysis of the functions of this part of the brain, there is little basis for correlation. It has not yet proved possible to reproduce in animals the pictures of basal ganglion disease encountered in human beings, although the recent experiments of Brown[272] are suggestive; a type of tremor not unlike that of Parkinsonism was produced in monkeys by lesions of the putamen combined with removal of extrapyramidal cortical fields.

CHAPTER XX

SOME HIGHER FUNCTIONS OF THE CEREBRAL CORTEX

The motor areas of the cerebral cortex are connected through the pyramidal and extrapyramidal tracts with the various lower motor neurons of the body. We have seen that the excitation of a localized area in the motor cortex may bring about a muscular movement which is coordinated, involves reciprocal inhibition, and develops through an orderly march in much the same way as does the reflex figure which arises from a cutaneous stimulation. These responses utilize the same motor mechanisms as the spinal reflexes do, and consequently come in competition with them for use of the final common paths. Consequently cerebral influences may modify profoundly reflex responses, reinforcing them when both affect the motor mechanism in the same way, inhibiting them when their actions are antagonistic. The inhibitory aspects of the cerebral influence are particularly prominent, and consequently many reflexes are elicited with greater certainty in animals from which the cerebrum has been removed. In this competition probably much the same factors determine which influence shall control the common path as govern which of two antagonistic spinal reflexes shall prevail. Cerebral influences are apparently prepotent over all but the most intense reflex responses to harmful stimuli and those which result from strongly affective sensations. We can, for example, inhibit the reflex withdrawal of the hand from hot water unless the pain is particularly intense. On the other hand, it is difficult to refrain from winking when the cornea becomes irritated. Within limits the respiratory movements may be controlled by the will, but when the stimulus to the respiratory center becomes intense, the breath can no longer be held.

The motor areas in the cortex are points at which many neurons from widely separated parts of the brain converge upon paths which lead to the lower motor neurons and their muscles. The corticifugal fibers consequently are common paths used in many diverse volitional responses of cortical origin. For their control many different influences come into competition, and the unpredictable nature of volitional response is no doubt due to the impossibility of determining which of the antagonistic elements in this competition will prevail.

The Relation of the Cerebrum to the Distance Receptors.—The development of the brain in the leading segments of the body is associated in all animals with the acquirement of the distance receptors of the head, i.e., the eye, ear, and olfactory organ. These sense organs serve to acquaint the organism with parts of its environment with which it has not yet come into immediate contact. They are suited to bring about responses which are anticipatory of the consequences of more direct contact with objects in the environment, that is, of the seizure and consumption of food, the appropriation of a mate, or the avoidance of objects which might prove harmful on closer contact. In order that responses toward distant objects may be made with discrimination, a mechanism has been evolved which apprehends the distant object not merely as a stimulus possessing a single quality, but as a "thing" built up of a number

of properties, and the response is determined by these properties as a group. Since the properties of such environmental objects appeal to a variety of receptors, the sensations aroused by each must be combined in the nervous system and built up into a definite concept by a process of association.

Moreover, since the response to the distant object is of an anticipatory nature, it must be made with reference to the past experience which the animal has had with objects presenting a similar group of properties. Consequently the results of contact with the object must be associated as part of the concept with the various properties which have appealed to the distance receptors, in order that when such an object enters the environment at a later time the results of the previous encounter may be recalled and behavior modified accordingly. In other words distant objects appeal to the nervous system by virtue of the meaning which is placed upon the particular combination of receptors which they excite, and the sensations which arise as a result. The nature of the response which is thus called forth depends on the memory of past experience with similar objects. For this reason the development of distance receptors is associated with the development of the cerebrum in which association and memory manifest themselves. The modification of behavior through the correlation of present and past experience is the process of learning, which is one of the chief characteristics by which responses influenced by the cerebrum are differentiated from those of the lower levels of the nervous system.

CONDITIONED REFLEXES

The modification of behavior in the higher animals which results from past experience is primarily due to the characteristics of the cerebral cortex. The responses of this structure are readily modified by previous experience and training, and by the associations which it forms between various stimulating objects and the consequences which result from its responses to them. It must be considered one of the greatest advances of modern physiology that Pavlov[304] has succeeded in developing methods by which the formation of these new responses on the part of the cerebral cortex can be studied by direct objective methods in animals.

The behavior of every animal depends in very large part on reflexes mediated through the spinal cord or brain stem which are inborn or develop invariably early in life and can in no sense be the result of training or experience. These reflexes include the responses required for standing, progression, simple defense reaction, the various responses involved in taking food, mastication, swallowing, defecation, and the like. They occur automatically as the result of appropriate forms of stimulation and thus allow the animal to behave in an appropriate way in the face of certain natural necessities. The previous history of the individual is not one of the conditions on which the character of these basic responses depends, and they are consequently called *unconditioned reflexes*. Modification of the conditions under which these inborn responses occur may be brought about as the result of experience or training, and these responses to new forms of stimuli are called *conditioned reflexes*. Many conditioned reflexes are formed naturally in the life of every animal; others may be artificially developed through processes of training.

The secretion of saliva which occurs when food is placed in the mouth of a dog is an example of an *unconditioned reflex* and is a response which has been

used extensively in studying the formation of conditioned reflexes. The secretion of saliva may be caused to occur as the result of any one of a great variety of stimuli which would not ordinarily call it forth. If, for example, every time food is presented to the dog, a particular sound is made, after a few repetitions it will be found that the occurrence of the sound alone is sufficient to cause the salivary secretion. Salivation now takes place as a *conditioned reflex* to an auditory stimulus which did not originally have any effect of this sort.

In developing such a connection between an unconditioned reflex response (salivation) and a conditioned stimulus (the sound), it is essential that the conditioned stimulus be applied at the same time or before the unconditioned stimulus (food). If it is applied after the giving of the food, no conditioned reflex is ever developed in response to the sound. On the other hand, if the conditioned stimulus is given a short time before the food is presented, a conditioned reflex may be developed in which the secretion of saliva always occurs after a delay equal to the time habitually occurring between the presentation of the conditioned stimulus and the food. Such reflexes are called *delayed reflexes.* In developing such delayed reflexes it is necessary first to form a conditioned reflex by the simultaneous presentation of the conditioned and unconditioned stimulus and then increase the time occurring between these stimuli either gradually or suddenly. The delay may be extended by these means to several minutes.

The study of conditioned reflexes has shown that *inhibition* is quite as important an aspect of cerebral activity as is *excitation. External inhibition* is produced according to Pavlov by any unusual stimulus which diverts the dog's attention at the time the conditioned stimulus is applied. It causes the conditioned reflex to fail to appear. The presence of a strange person in the room or an unexpected sound may inhibit well-formed conditioned reflexes which, however, reappear in normal fashion when the disturbing influence is removed. *Internal inhibition* designates a more permanent form of inhibitory effect. Thus, if a conditioned stimulus is repeated several times without being reinforced occasionally by the application of the unconditioned stimulus, that is, without the occasional administration of food in the case of the salivary reflex, the conditioned reflex will become weaker and will ultimately disappear. The disappearance of the conditioned reflex is, under these circumstances, due to an inhibitory effect and not to the permanent destruction of the conditioned reflex because, after a period of rest, the conditioned reflex will reappear with its original vigor.

The delay in the response of a delayed reflex may also be shown to be due to a temporary inhibitory phenomenon which intervenes between the application of the stimulus and the conditioned response. This is shown by the fact that the inhibition can be interrupted by external inhibition. A sudden noise or other strange stimulus occurring during the refractory period of a delayed reflex causes the conditioned response to begin at once. The inhibitory process has been interrupted by the unusual stimulus allowing the conditioned reflex to complete itself without further delay.

It is possible to develop inhibitory conditioned reflexes which show quite as definite a relation to the conditioned stimulus as do the reflexes leading to positive responses. Suppose a conditioned salivary reflex has been established in response to a certain sound. A different type of stimulus—let us say a flash-

ing light—may now be made to inhibit the salivary response to the sound. This is done in the following way: Every time the sound is used alone as a stimulus, food is given to reinforce the conditioned reflex. Occasionally the light is flashed at the same time the sound is produced and on these occasions no food is given. Soon the animal distinguishes between the sound alone and the sound accompanied by the light. The sound alone will continue to excite the conditioned response, but when the sound is accompanied by the light, the response is inhibited.

The Analyzing Function of the Cerebral Hemispheres.—The method of studying conditioned reflexes devised by Pavlov not only provides a means of studying how associations are formed between various stimuli and the basic unconditioned reflexes, but it also enables an examination to be made of how the cerebrum comes to differentiate between various kinds of stimuli. The primary analysis of stimuli is made, of course, by the sense organs themselves, each of which responds with a characteristically low threshold to some particular form of stimulus and passes on the disturbance to the brain through definite sensory tracts terminating ultimately in more or less definite regions of the brain. The study of conditioned reflexes demonstrates that the cerebrum carries out a further analysis and synthesis of these nerve impulses, distinguishing between them with greater exactitude as the result of experience and training. By this means the scope and limits of the analyzing functions in different animals can be exactly determined. When a conditioned reflex is first developed, the animal does not distinguish closely between somewhat similar stimuli. A conditioned reflex to a note of one pitch may be called out by notes of rather different pitch. If tactile stimulation of one skin region is caused to elicit a conditioned reflex, the tactile stimulation of a neighboring area will also be found effective. The response is generalized in the sense that it occurs when different sense organs of the same general type are excited. This is an example of the synthetic action of the cerebral cortex. Discrimination between different forms of allied stimuli appears to be developed by the formation of internal inhibitions conditioned upon one of the stimuli which is to be differentiated from another. Thus, if a conditioned salivary reflex is called out by a note of 800 d.v., a note of higher pitch will also elicit the response. By repeating the higher note without ever reinforcing the reflex by the simultaneous administration of food, while the note of 800 d.v. is constantly reinforced, the response to the higher note will become inhibited. Once discrimination is established in this way between rather dissimilar stimuli, the inhibition may be caused to extend to stimuli more and more like that which remains the source of the positive conditioned response. In this way dogs may be shown to discriminate between a pitch of 800 d.v. and 812 d.v. They can readily distinguish shades of gray cardboard which appear almost alike to the human eye, and can hear and distinguish sounds of a pitch quite beyond the range of the human ear. On the other hand, they appear almost unable to distinguish colors and are apparently nearly color-blind. In this way much can be learned about the sensory processes in lower animals.

That discrimination between similar stimuli is due to the establishment of an inhibitory process in association with one of them is indicated by the fact that such inhibitory processes may be interrupted by unusual stimuli (external inhibition) just as in the case of the inhibition which is responsible for delayed

reflexes. An animal which has learned to respond in a positive way to a note of 800 d.v. and to give no response to a note of 816 d.v. will respond positively to the latter note if it is unexpectedly accompanied by some other strange stimulus.

Pavlov has extended the idea of internal inhibition to account for sleep and hypnosis and certain types of neuroses. For a discussion of these subjects his book on *Conditioned Reflexes*[304] should be consulted.

LOCALIZATION OF CORTICAL FUNCTION IN LEARNING

Pavlov was inclined to believe that after removal of the entire cerebral cortex of both hemispheres all conditioned responses disappear and cannot be reacquired, although the unconditioned responses on which they are built remain practically normal. But recent work has shown quite definitely that certain conditioned reflexes can be established in decorticate dogs (Zeliony; Culler and Mettler) and wholly decorticate cats (Bromiley), although with no great readiness. It is true that under ordinary conditions of existence such animals do not develop adaptive modes of response; conditioning occurs only as the result of subjecting them to special experimental procedures. There can be no doubt that in the higher mammals the process of conditioning is predominantly a cortical process.

The study of conditioned reflexes may be applied to examination of the functions of different anatomical areas of the cerebral cortex. When localized portions are removed, obliterating one of the principal sensory areas, all conditioned reflexes dependent upon the kind of sensation involved disappear and for a period following the operation cannot be reestablished. Thus, the removal of the occipital lobes interferes with all but the simplest conditioned reflexes to light; destruction of the temporal lobes obliterates reflexes conditioned upon sound. Some time after the operation, however, conditioned reflexes depending on the sensation associated with the injured area may be reestablished, showing that the analyzing function of the brain is not entirely localized in this area. Thus, dogs in which the entire posterior halves of the cerebral cortices are removed may still develop conditioned reflexes to sound and light, although the sensory areas of sight and hearing in the occipital and temporal lobes are entirely absent. Such animals can also be trained to distinguish between differences in intensity of light, between sounds of different pitch, and between simple visual patterns. They cannot, on the other hand, recognize and distinguish more complex combinations of sounds or visual images, such as musical chords or scales and the appearance of various objects. Consequently they do not respond to their names or seem to recognize the persons or objects about them. It has been concluded from these studies that in the cortex, besides the special sensory areas or analyzers, there must exist some extensions of these analyzers dispersed more widely throughout the cortex. On the other hand, in view of the fact that conditioned responses may be formed in wholly decorticate cats and dogs, it does not seem necessary to attribute these results to any such hypothetical extension of the analyzer. It is quite possible that the remaining cortex contributes an entirely nonspecific type of facilitation to the subcortical portion of the analyzer which is really the site of the elaboration of the conditioned response.

Finally, Pavlov has concluded that there is no localized region or center within the cerebrum on which the process of association or conditioning *in itself* depends. He thus disposes of the doctrine of the existence of special association centers distinct from the special analyzing centers associated with the various sense organs. No matter what part of the cortex is destroyed the remaining portions are capable of developing conditioned reflexes with all their peculiarities, and the only limitations imposed are in the analyzing and synthesizing powers in connection with the particular kinds of sensory phenomena centered in the damaged region.

The problem of the localization of the cortical mechanisms which underlie the acquisition of new motor acts has been studied by Lashley[298, 299] in a somewhat different manner. Making extensive use of the white rat Lashley has studied quantitatively the effects of cortical lesions upon the formation and retention of various motor habits. One important conclusion which may be drawn from his results is that it is necessary to recognize the existence of degrees of localization of function in the cortex.

A surprising lack of specific localization was found by Lashley when he studied the effects of cortical lesions on the amount of practice necessary for rats to learn to thread a complex maze. A slowing of the process appeared no matter where the cortical lesion was made, but showed a high correlation with the percentage of cortex destroyed. Removal of equal amounts of tissue from different cortical projection areas (motor, somatic sensory, auditory, and visual) produced equal degrees of retardation. Further, it was found that the contribution normally made by any one area is nonspecific. For example, the visual cortex (area striata) exerts an influence in the formation of this habit which is not dependent on vision, for blinding did not interfere with the rate of learning the maze, whereas destruction of the visual cortex in blinded rats did produce retardation. It appears that although one of the sensory impressions which enable the normal animal to acquire this habit may be visual, the area striata exerts an influence which is not dependent on any visual stimulus. The results show that this same influence emanates to an equal extent from each part of the cortex. To this Lashley has given the name "mass action."

Another example of mass action is seen in the results obtained by Lashley when he tested the influence of the visual area on the retention of a habit of brightness discrimination. The rats were trained to enter an illuminated compartment and to avoid a darkened compartment. This simple visual habit was formed with the same speed in rats from which the entire visual cortex had been removed as in normal rats. This fact taken in conjunction with the evidence that no cortical areas other than the visual cortex receive fibers from the lateral geniculate bodies makes it reasonable to conclude that brightness discrimination in the rat depends on subcortical mechanisms. Once the animal had been trained, however, total ablation of the striate areas caused it completely to lose the habit (amnesia). Such animals could relearn to make the discrimination, but they required just as much practice as they did for the initial learning before operation. If only a fraction of the visual areas was destroyed, the rat relearned more rapidly than when all was removed. The amount of practice necessary to reestablish the habit was found to be closely proportional to the extent of the injury and quite independent of its locus within the visual cortex. This area apparently acts as a unit in providing the retention

of a function which is acquired through the mediation of a subcortical mechanism. In this case there is a certain degree of localization, for the visual areas are the only parts of the cortex which exert this effect.

That subcortical mechanisms suffice for the function of brightness discrimination in an animal higher in the mammalian scale than the rat, namely the dog, has been demonstrated by Marquis.[300] After bilateral removal of the area striata the dog appeared totally blind; he collided with objects in his path and neither blinked nor flinched in response to threatening movements. In spite of these profound visual deficiencies such a dog may be trained to discriminate between a dim and a bright light. It was found that the threshold for this simple discrimination was raised only slightly by the extirpation of the visual cortices. Removal of all the visual cortex after the habit had been formed abolished it, but it could be relearned with slightly less practice than was required for its initial formation. Quite similar results have been obtained by Marquis and Hilgard in a study of monkeys from which the occipital lobes had been removed. Further information on this important subject is given in Jacobsen's recent review.[295]

When an acquired response depends upon the detailed characteristics of a stimulus, the cortical mechanism essential to its execution is highly specialized, differentiated, and spatially distinct. Thus when Lashley turned his attention to the experimental investigation of cortical function in pattern vision, he discovered one of the most striking examples of strict localization of function. Bilateral destruction of a very small region in the lateral part of the visual area completely and permanently abolishes the capacity to discriminate between patterns as effectively as destruction of the entire occipital cortex or interruption of the optic radiations. Lesions in the medial portions of the striate areas and extensive destructions in the motor and somatic sensory zones had no effect on this more specialized visual function.

Lashley's studies of the cortical mechanisms involved in various acquired responses to visual stimuli give us a picture of a cortical area in which, for some activities the efficiency of performance is simply proportional to the quantity of tissue available, while for other more complex functions the different parts of the area contribute specifically and diversely to the reaction. His experiments have also made it clear that when a response develops on the basis of a discrimination between two similar stimuli, the adequacy of the stimulation depends not upon the activation of any specific sensory cells, but upon the pattern of excitation. If a rat is trained to jump to a white erect triangle and to avoid an inverted one, it will still react correctly when for the first time it is confronted with mere outlines of these figures in smaller size. Lashley points out that here "none of the retinal cells and consequently none of the cells of the projection area which were stimulated by the contour of the figures during training are similarly stimulated by the contours of the test figures." It must be admitted that it would be extremely difficult, not to say impossible, to account for such conditions of response on the basis of conduction of impulses over neural paths and of specific connections between the sensory surface and the effector mechanisms. Although there is available no direct experimental evidence to show that the central nervous system employs any other form of conduction of excitation than the nerve impulse, it is only reasonable, in the light of such facts, to view this possibility with an open mind.

ELECTRICAL SIGNS OF CORTICAL ACTIVITY: THE ELECTROENCEPHALOGRAM

By the study of the electrical changes in muscle and nerve much precise information has been accumulated concerning the functional properties of these peripheral structures. This has been possible largely because of the simple arrangement of more or less parallel fibers in bundles, a circumstance which permits analysis of the conditions underlying a difference of potential between two electrodes placed directly on the nerve or muscle. In the central nervous system the complex distribution of axons and the profuse interpolation of cell bodies, dendrites and synapses makes analysis of activity by electrical means much more difficult. Furthermore, the electrical characteristics of these central structures are not known with any great certainty. The electrical changes which can be recorded from the central nervous system present features which differ, at least in a superficial way, from those of the action potentials of peripheral nerve. We have already encountered the cord potentials (page 103) and the cortical potentials which occur as definite responses to stimulation of cutaneous receptors (page 209). The former probably represent the summed spikes and after-potentials of internuncial neurons. The origin of the latter is at present a subject for conjecture and further study.

Another striking electrical sign of activity in the central nervous system is the series of slow waves of large amplitude which appear to arise spontaneously in the central gray matter. The cerebral cortex is one source of these, but they are also found in the thalamus and cerebellum. As first shown by Berger, some of these potentials are of such magnitude that they can be recorded by placing electrodes on the scalp over the unopened skull. Records obtained in this way are most generally called "electroencephalograms," although Davis and Davis[277] use the term "cortical electrogram" on the assumption, which appears to be perfectly correct, that the potentials arise mainly in the cerebral cortex. Sometimes these waves are spoken of as brain "action potentials," but in view of the almost total lack of information of their fundamental nature it seems quite inappropriate to apply to them a term which has such a definite and established meaning.

Studies of the waves of the electroencephalogram have so far proved of interest chiefly by showing that there is some correlation between these signs of neural activity and different physiological, psychic and pathological states. The usual record shows waves which appear at certain rather definite frequencies. The most prominent rhythm is one which ranges from 8 to 13 and averages 10 waves a second. This is sometimes called the "Berger rhythm," but has more generally come to be known as the *alpha rhythm*. A secondary series of potentials with waves lower in voltage but higher in frequency (17 to 50 a second) is called the *beta rhythm*. These waves may be superimposed on the alpha rhythm, or may be seen continuing when the latter has dropped out. Certain average characteristics have been ascertained for all normal individuals. The alpha waves are usually most prominent when the subject is sitting or lying quietly, with eyes closed and mind at ease. Under these conditions they may run continuously with only slight variations in rate. Any considerable mental effort tends to depress them and intense concentration or emotional excitement causes their complete disappearance. In light sleep the

alpha waves tend to become slower, larger and less regular in form and frequency. In deep sleep activity is usually absent, although irregular volleys of slow large waves may occur at intervals. These characteristics are illustrated in Fig. 76. In the waking state the beta waves are more stable than the alpha, and on them emotional excitement and the process of attention have less effect.

As a result of extensive observations carried out under certain standard conditions, Davis and Davis[277] have concluded that "different persons show different patterns of activity, but each reproduces his own characteristics." Thus it was found that when a subject is tested a second time after an interval of weeks or months, but under the same conditions, he yields a record which resembles the first very closely. A most interesting finding is that identical twins show similar patterns, the records from one twin resembling those from the other "as closely as the records of the same person on successive tests."

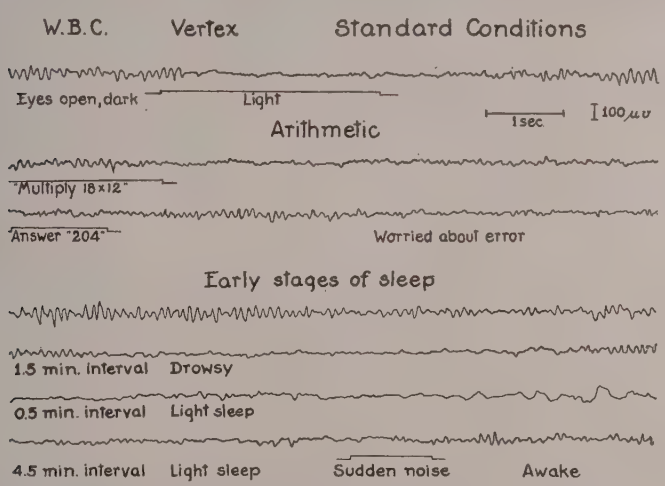


Fig. 76.—Electroencephalograms (cortical electrograms) of a normal man aged sixty-four, recorded from the midline of the occiput, about 2 cm. above the inion. Calibrations of time and sensitivity are given below the first record for 1 second and 100 microvolts. This subject showed a dominant alpha rhythm, suppressed by illumination. The third record is continuous with the second. (From Davis and Davis: Arch. Neurol. & Psychiat. 36: 214, 1936.)

The electroencephalogram has recently become an object of interest to both the neurologist and the psychiatrist because of indications that it may be of service in the diagnosis and description of diseases of the central nervous system. In the case of one disorder, epilepsy, the spontaneous potential waves show the most dramatic changes. Indeed the onset of an epileptic attack of the grand mal type is indicated in the electroencephalogram by changes in amplitude and frequency of the alpha waves even before it becomes apparent to clinical observation. A quieting of the rhythm occurs during the early tonic phase of the fit, but with the beginning of the clonic convulsive movements the waves attain amplitudes ten to twenty times normal. Evidence has been obtained to show that it is possible, by taking a series of records from different head regions, to determine topographically the cortical origin of the attack.[296]

The topographical origin of the cortical potentials is a question which has received some attention. Adrian and his collaborators[264, 265] developed the thesis that the occipital region is the source of the alpha waves, but others find them over other portions of the cortex and have even recorded them from the dura over the frontal lobe. There is some evidence

indicating that these extra-occipital alpha waves may originate from almost any part of the cortex. It is said that beta waves predominate in the precentral region of the head (Jasper and Andrews).

The Composition of the Waves of the Electroencephalogram.—The electroencephalogram has sometimes been compared to the electrocardiogram (see Chapter XXX). The two are alike in being electrical signs of activity in internal organs recorded by leads applied to the surface of the body. With this the analogy must, at least for the present, be brought to an abrupt end. Analysis by a variety of methods has shown a definite correlation between the myocardial activity underlying the events of the cardiac cycle and the several components of the electrocardiogram. No such precise reference points have been made out for the electroencephalogram. While the examination of the latter may yield interesting and suggestive results it is not likely to contribute fundamentally to our knowledge of central nervous activity until the composition of each wave is known. For instance, it would be desirable to know whether an alpha wave lasting from 50 to 120 msec. is an approximate picture of the progress of an event in a single cortical neuron. If it is, the large voltage of the recorded waves (5 to 100 microvolts) can be explained as the result of simple addition of the potentials of many cortical neurons discharging synchronously. Many workers have attributed the waves to spontaneous beating of the cortical cells. Adrian and Matthews[264] who have claimed that the alpha rhythm represents the spontaneous synchronized beating of cells in the visual area of the occipital lobe, point out the very close resemblance of this rhythm to the electrical pulsations given by the vertebrate retina and the optic ganglion of invertebrates. In each case when the eye is uniformly illuminated or in darkness "the neurons can pulsate synchronously because the degree of excitation is the same for all of them; but non-uniform illumination of medium brightness makes the synchronous beat impossible and abolishes the rhythmic potential waves."

CHAPTER XXI

THE PHYSIOLOGY OF SLEEP

From the point of view of comparative physiology sleep appears to be a special example of a very general phenomenon. All plants and animals show some periodicity of rest and activity. In the lower animals, even when a well organized central nervous system is present, these alternations may not depend on the brain or head ganglion. For example, when an earthworm is cut in two, each half continues to exhibit, during each twenty-four hours, the four periods of rest which characterize the behavior of the intact animal.[327] How intimate the relation may be between the rest periods of lower animals and the phenomenon which we designate as sleep in birds and mammals is not known. It is clear, however, that in the case of the latter group we are concerned with *cerebral* sleep. When the spinal cord of a mammal is isolated from the brain by transection nothing resembling periodic sleep occurs in the part of the body innervated by the segments aboral to the separation, but the forepart of the animal continues to show typical periodic sleeping.

No satisfactory short definition of sleep is possible. This is the result of the failure of investigation so far to secure any direct evidence of the actual cerebral changes which underlie this particular form of rest. We can describe sleep in terms of its concomitants, study the disorders of sleep and the effects of loss of sleep, and we can perhaps gain some impression of its nature from the results of experimental efforts to induce it, but it remains to determine the real basis of sleep. The outward signs of sleep are so well recognized that they require no special description. There are certain criteria which, taken together, may be used to differentiate sleep from other conditions of unconsciousness, such as coma, narcosis and hypnosis. Kleitman[327] lists as the more important of these: (1) a loss of critical reactivity to events in the environment; (2) an increased threshold of reflex irritability and general sensibility; and (3) a capacity to be aroused or brought back to a state of wakefulness. In contrast to the inactivity of coma and narcosis sleep is a change which is easily reversible.

Bodily Changes Accompanying Sleep.—A large number of studies have been made of the physiological concomitants of sleep, apparently in the hope that some finding might prove to be the key to an explanation of the phenomenon.

Considerable attention has been devoted to circulatory changes. All observers are agreed that the heart rate decreases during sleep and many have reported a fall in arterial pressure. The earlier studies were largely concerned with the detection of changes in the distribution of blood in the body. Several physiologists, chief among them Mosso and Howell, brought forth evidence showing that during sleep the volume of the hand, arm or foot increases, a change denoting dilatation of peripheral blood vessels.[325] In 1881 Mosso concluded, as a result of observations made on patients with skull defects, that peripheral vasodilatation is accompanied by a diminution in brain volume. These and

other experiments led to the theory that sleep is due to cerebral anemia. But this pleasantly simple explanation subsequently encountered serious contradictions. Shepard, for example, reported that in man there is actually an increase in brain volume during sleep, while waking is accompanied by signs of cerebral vasoconstriction. In observations on puppies Kleitman[327] could detect no changes in the appearance of the pial vessels with the onset of sleep or with awakening. Gibbs, Gibbs and Lennox[319] found no significant changes in the volume flow in the internal jugular vein of patients when the latter fell asleep or awoke, and concluded that this observation puts to rest the vascular theory of sleep "that has too long haunted textbooks and neurological literature." Certainly the evidence is definitely against the occurrence of generalized cerebral anemia during sleep. Whether sleep may be correlated with some local vascular change in the brain involving so small an area that it could not be detected by ordinary methods is a question which should perhaps be kept in mind. On the whole the circulatory changes which accompany sleep may be regarded as the results of prolonged physical rest.

There is general agreement that the excitability of many reflexes and responses is diminished during sleep. The knee jerk and other proprioceptive responses decrease and may finally disappear. Kleitman found that in puppies the labyrinthine righting reaction acting on the neck is lost in sound sleep. Cutaneous reflexes are better preserved. Facial grimaces and arm movements adapted to eliminate the source of stimulation are easily evoked by brushing the cheek. Light constricts the pupil and various extraneous stimuli dilate it. Changes in heart rate which occur during sleep are probably of reflex origin.

The depth of sleep is commonly determined by finding the intensity of a stimulus, most often an auditory one, which is just necessary to awaken the subject. By applying the test at intervals during the period of sleep results are obtained which can be expressed by a curve in which the strength of the effective stimulus is plotted against the time from the onset of sleep. Most of the curves obtained in this way indicate that sleep attains its greatest depth about an hour after it begins, and that from the third hour onward it is very light. There can be no doubt that sleep varies in intensity, but there are reasons for believing that the matter is not quite so simple as these curves suggest. For one thing, there are marked individual differences.

The Importance of a Decrease in Afferent Impulses.—Common experience suggests that a decrease in the number of afferent impulses reaching the central nervous system must be of considerable importance in determining the onset and maintenance of sleep. Kleitman[327] has emphasized the role played by muscular relaxation and the consequent diminution in proprioceptive stimulation. He points out that sleep is easily induced, even in the absence of fatigue, when a person or an animal is made to relax. It is relatively easy to rid ourselves of sensations of touch, taste, smell, sight and hearing, but even in resting postures muscle tone is sufficient to maintain some bombardment of the brain with afferent impulses from proprioceptors. It will be recalled that the sense organs in muscle which respond to stretch show little adaptation, while the cutaneous receptors subserving touch and pressure soon cease activity when the stimulus is kept constant (page 67). Therefore when one lies down in a quiet and darkened room the greater part of the stimuli falling on the central

nervous system are afferent impulses from muscle proprioceptors. As shown by Kleitman, the reduction of these through muscular relaxation, whether intentional or unintentional, tends to bring on sleep.

The Part Played by Fatigue.—When fatigue is great, sleep is apt to come on with great readiness. This common experience has given rise to the theory that sleep is due to the action of the chemical products of muscular activity. The suggestion has been made that lactic acid circulating in the blood may induce sleep. There is, however, not the slightest evidence in favor of this proposal. The fact that sleep can occur in the absence of fatigue shows that any effect which may be exerted by fatigue substances must be of secondary importance. Until some one supplies experimental facts showing that lactic acid or some other product of muscular activity has a soporific action this theory of a chemical factor should be relegated to a list of minor possibilities. Kleitman suggests that sleep is due to fatigue of the neuromuscular mechanism concerned in the maintenance of muscle tone. This mechanism, however, is one which operates in a manner specifically designed to avoid fatigue. The basis of muscle tone is asynchronous activity in a limited number of muscle units, at a frequency so slow that only a series of twitches or an incomplete tetanic contraction results. Muscle responding in this way does not fatigue, nor is there any evidence that the proprioceptors stimulated by the tonic activity are fatigable; certainly they adapt very slowly. It is true, however, that when one attempts to prolong a period of wakefulness sleep can best be avoided by indulgence in muscular activity. The exertion probably acts by increasing enormously the number of sensory impressions and possibly by bringing about certain circulatory adjustments.

Allied to the chemical theory of sleep is that which invokes a specific cerebral toxin as the cause of the condition. In his excellent monograph on sleep Piéron[331] advanced the view that a "hypnotoxin" is produced during wakefulness and acts as a soporific to produce or facilitate sleep. Piéron offered some experimental evidence in support of his contention. It was found that when cerebrospinal fluid from a fatigued animal is injected into the cerebral ventricles of a normal animal, the latter shows signs of drowsiness and falls "asleep." In a recent reexamination of the hypnotoxin theory of sleep Ivy and Schnedorf[326] confirmed Piéron's observation, but were unable unequivocally to confirm his interpretation of it. When 8 ml. of cerebrospinal fluid were withdrawn from the cisterna magna of a normal dog and replaced by an equal volume of fluid from a sleep-deprived dog the former animal became drowsy and showed marked depression for 5-8 hours during which time it could be aroused only with difficulty. The depression was accompanied by a rise in temperature. While simple withdrawal of fluid did not produce these effects, the reinjection of normal fluid did, although in no case was the depression as great as the greatest depression caused by injection of fluid from the dogs which had been deprived of sleep. Thus, there remains much uncertainty as to the real significance of Piéron's findings.

Cerebral Mechanisms Underlying Sleep.—It has already been pointed out that in the higher animals sleep is distinctly a manifestation of cerebral change. A full explanation of the phenomenon will necessarily consist largely of a description of the operation of central nervous mechanisms. It is reasonable to suppose that we would now know far more about sleep if investigators had earlier begun to address their inquiries more particularly to the central organ instead of devoting the greater part of their attention to peripheral phenomena which are either the results of sleep or merely serve to set the stage for the act of sleep. In recent years some progress has been made in this direction.

Pavlov[304] attempted to explain sleep on the basis of the phenomenon of internal inhibition of conditioned reflexes (page 233). Throughout his studies of the process of conditioning in dogs it was noticed that whenever internal inhibition was taking place drowsiness and even deep sleep tended to appear. Thus it was found that when a conditioned reflex was being extinguished by repeating the conditioned without the unconditioned stimulus some animals showed "a great dullness as compared with the normal state before the extinction." The same thing was seen to a much greater extent in the development of differentiation, the basis of which is internal inhibition. Pavlov considered that sleep is brought on when internal inhibition, set up in the cortical component of one analyzer, irradiates to other analyzers. Kleitman[327] regards Pavlov's explanation as quite unsatisfactory, and refers to the readiness with which dogs placed in stands similar to those used by Pavlov go to sleep under circumstances which apparently do not involve any conditioning. From his own experiments on conditioned reflexes he cites the case of a "dog that fell asleep habitually *while* actively secreting saliva as a conditioned reflex." Yet it seems possible that internal inhibition may have been operating in some other analyzer than the one utilized in the salivary conditioned reflex of this experiment. It seems fair to say that while Pavlov's theory of sleep, like all other theories of sleep, is incomplete, it has much to recommend it and should not be lightly dismissed until additional work has clearly shown it to be untenable.

In considering the cerebral mechanisms involved in sleep it is customary to direct attention to the cerebral cortex. But all who have studied decorticate cats and dogs agree that they display states of rest which, at least superficially, are indistinguishable from sleep in normal animals of the same species. In his review of 1929 Kleitman quite properly raised the question whether such preparations are ever really awake and whether therefore one can speak of their sleeping. A little later Kleitman and Camille[328] put this question to a careful experimental test and as a result concluded that the decorticate dog actually does sleep. They noted that during "sleep" the animal not only assumes the postures characteristic of the sleeping normal dog, but shows the heightened threshold of reflex excitability which distinguishes sleep from mere inactivity. The chief effect that decortication has on sleep in the dog is to convert the periodicity of wakefulness and sleep from the monophasic diurnal type (long sleep at night with only short naps in the daytime) to the polyphasic type characteristic of puppies. In the latter there are several periods of sleep in twenty-four hours.

The fact that true sleep occurs in decorticate animals places some emphasis on subcortical sleep mechanisms. That certain parts of the brain stem have something to do with sleep has long been suspected. The earliest suggestion of such a relationship seems to have come from Mauthner in 1890. During that and the preceding year a disease which later came to be known as lethargic encephalitis appeared in epidemic form in southern Europe. Mauthner was so impressed with the association, in patients with this disorder, of hypersomnia and oculomotor paralysis that he developed the idea that the provocative lesion must lie in the gray matter surrounding the sylvian aqueduct. Von Economo concluded from his classical study of this disease carried out during the epidemic of 1916-1917 that its outstanding symptom, prolonged sleep, is related to the localization of an inflammatory process in the zone of transition between

diencephalon and mesencephalon.[333] While the lesions of the disease may be fairly widespread in the brain, there is a definite tendency for them to be fairly well restricted to this particular region. The somnolence of encephalitis lethargica is apparently closely allied to normal sleep, that is, it is a true hypersomnia, for even when it is deep and lasts for days, weeks or months, the patient can always be awakened. In this it differs strikingly from the horde of clinical conditions in which consciousness is irreversibly lost for considerable periods of time. Von Economo claimed that the study of this disease demonstrates the existence of a sleep regulating "center" in the caudal hypothalamus and the rostral portion of the midbrain. Lhermitte and Tournay,[329] also on the basis of clinical studies, came to essentially the same conclusion.

There is much detailed experimental evidence indicating the presence of a subcortical mechanism which is somehow intimately concerned in the production of sleep. The dramatic results obtained by Hess[322-324] appeared to show that sleep can be produced by excitation of subcortical regions. By first placing electrodes in the brain stems of cats and then later, after recovery from the operation, stimulating by means of a current having certain characteristics, Hess produced a state which in the nature of its onset and in many particulars was indistinguishable from normal sleep. These results have been accepted by many as proving the correctness of the view of Pavlov that sleep is an active inhibition of the cortex; it has been supposed that the stimulation of a subcortical mechanism inhibits the cortex in much the same way that the vagus nerves inhibit the heart. However, Harrison,[321] using the type of current recommended by Hess in a large series of cats, did obtain somnolence, but only when lesions were produced, as shown by microscopical examination of the brain. Excitement was produced in many animals and significantly these did not show lesions. The conclusion was drawn that "when sleep may be caused by passage of electric currents through the brain stem, it is the destructive effects of the current and not stimulating factors that are responsible for the somnolence" (Harrison[320]).

Several lines of evidence suggest that the hypothalamus contains an important part of the central neural mechanism involved in sleep. The somnolence obtained by Harrison was the result of injury by passage of current through the lateral hypothalamic area. On the basis of a hypothesis, which is probably incorrect, namely, that during sleep calcium leaves the blood and enters the brain substance, Demole[317] tested the effects of intracerebral injections of calcium. He found that injections of small amounts of $CaCl_2$ into the gray matter situated above and behind the optic chiasm or into the tuber cinereum cause in cats a reversible condition which closely resembles sleep in all its main features. Demole also reported that injection of a solution of KCl into the same region causes either stupor, muscular hypertonia or signs of motor excitation, but not sleep. Berggren and Moberg[316] confirmed the observations of Demole as regards the effect of $CaCl_2$, but reported that injection of KCl or simple puncture was just as effective in producing somnolence or sleep. They located the "sleep center" in the infundibular portion of the hypothalamus. Marinesco, Sager and Kreindler[330] carried out similar experiments, which were well controlled histologically, and came to the conclusion that mechanical injury or anodal polarization of the walls of the third ventricle is the essential condition for the experimental production of sleep in this manner. It should be pointed out that each of these three groups of workers insists that the somnolence which they were able to

induce was in every important respect like normal sleep. It is this feature of the work which makes their results especially worthy of attention. In the light of Harrison's results and those to be mentioned in the next paragraph, the procedures which these investigators used were effective in producing sleep because they depressed or injured the hypothalamic region.

In chronic well-controlled experiments on monkeys Ranson[230, 257] has demonstrated that lesions of the hypothalamus may render the animals somnolent, usually for only a few days, but occasionally for weeks. The effective lesions were ones placed on each side at a locus where stimulation causes signs of anger (page 196). The monkeys become tractable and cannot be aroused to display the vigorous emotional behavior which characterizes the normal animal. It is significant that Ranson found that lesions confined to the thalamus do not cause somnolence. One might expect that thalamic damage, by interfering with the sensory pathways to the cortex, would predispose an animal to sleep. Indeed Spiegel and Inaba[332] have claimed that in dogs and rabbits injuries of the thalami are far more productive of sleep than are lesions in the central gray around the aqueduct and third ventricle. They conclude that the retention of a normal waking condition depends on the integrity of the thalamus, a state of sleep supervening when these sensory nuclei are removed. The results obtained by Ranson appear to contradict this thesis and again emphasize the hypothalamus. Possibly hypothalamic injuries bring on a tendency to sleep by excluding the central mechanism which elaborates emotional behavior of the rage type (page 196).

On the basis of the evidence available one must suppose that in the normal animal the cerebral mechanisms concerned in sleep are both cortical and subcortical and that the two are intimately related. It may even be that the chief function of these is to keep the animal awake and that sleep represents their inactivity. The fact that true sleep occurs in decorticate animals indicates that whatever the mechanism may be it must also influence the brain stem.

PART II

THE SPECIAL SENSES

By J. M. D. Olmsted

CHAPTER XXII

THE EYE AS AN OPTICAL INSTRUMENT

Refraction in the Schematic Eye.—Rays of light passing from one medium to another of different optical density are bent or refracted, if from a rarer to a denser medium, toward the perpendicular, if from a denser to a rarer medium, away from the perpendicular. The pathway taken by light rays in traversing the eye from the cornea to the retina, can be determined in exactly the same manner as for any other optical instrument, such as the camera, telescope, or microscope. The index of refraction, i.e., the ratio between the angles of incidence and refraction, is approximately the same for the cornea, aqueous humor and vitreous humor, but these parts of the eye are all optically more dense than the air, and rarer than the lens. Hence refraction will take place at the anterior surface of the cornea, and at both the anterior and posterior faces of the lens. Matters can be simplified in an attempt to follow the course of the light rays through the eye, and a sufficient degree of accuracy still be preserved, if we imagine that the light rays are bent only once at a single convex surface, situated in the aqueous humor (the schematic eye). The center of curvature of this imaginary surface lies 7.3 mm. from the anterior surface of the cornea.

In the emmetropic or normal eye at rest, i.e., when focused on a distant object, parallel rays come to a focus 15.5 mm. back of the center of curvature of the imaginary convex surface in the reduced or schematic eye. This proves to be the distance at which the retina is situated. Therefore, the light rays under these conditions come to a focus on the retina. But if the source of light is moved nearer the lens, the rays emerging from the lens diverge farther and farther.

In either case the image is inverted, reversed, smaller than the object, and projected on to a curved surface (Fig. 77).

This can be demonstrated experimentally by removing the outer coats of a fresh ox-eye over a small window at the back and placing a piece of transparent tissue paper over the opening. It is found that the image of objects in front of the eye is inverted and reversed on the paper. A simple experiment on oneself demonstrates this reversal. Close the eyes and direct the right eye toward the nose; pressure with the finger on the temporal side of the right eyeball will cause a bright ring to appear on the nasal side. This can only mean that stimulation of the retina on the temporal side produces an effect which appears to come from the nasal side of the visual field. The relation of the blind spot in the visual field to the position of the optic disc in the eyeball, and the relation of other gaps in the visual field to scotomas in known parts of the retina are further proofs of the reversed relation of visual field and points on the retina.

Accommodation.—When the emmetropic eye is at rest and the optical system is so arranged that distant or parallel light rays from a fixated distant object come to a focus on the retina at the macula, it is said to be accommodated for far vision. For each point of the object there will be a point in the image on the retina and rays coming from the right side of the object fall upon the left side of the retina and vice versa, and those from the top of the object fall on the lower part of the retina and vice versa. Rays from an object nearer than twenty feet must under these conditions come to a focus behind the retina. This would mean that the different rays coming from a single point in the object would not converge to a single point on the retina, but each point of the object would

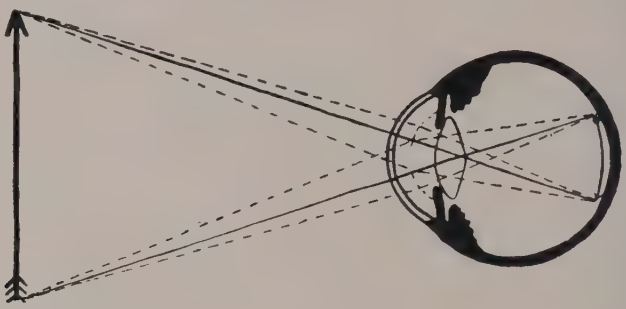


Fig. 77.—Formation of retinal image in the schematic eye.

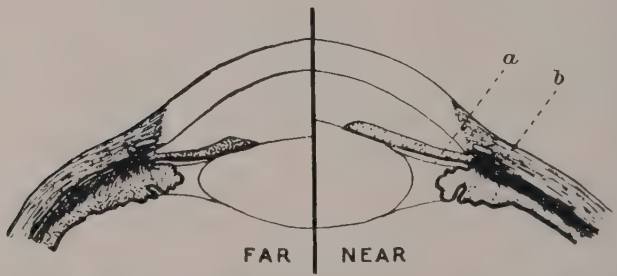


Fig. 78.—To illustrate accommodation: *a*, suspensory ligament; *b*, ciliary body.

be represented by a circular area of diffused light and the areas for neighboring points of the object would overlap. Hence the object would be seen indistinctly. For distinct near vision, therefore, the optical system must change in such a way that these diverging rays come to a focus on and not behind the retina. This change is known as "accommodation for near vision" and involves muscular effort (Fig. 78).

The lens is a viscous body enclosed in an elastic capsule and during rest or accommodation for far vision is kept in a flattened state by the pull of the fibers on the suspensory ligament, the zonule of Zinn, which attaches the capsule to the ciliary body. The constant intraocular pressure present in the eye keeps the coats of the eyeball distended, so that the ciliary body is pulled backward and the fibers of the suspensory ligament remain taut. The generally accepted

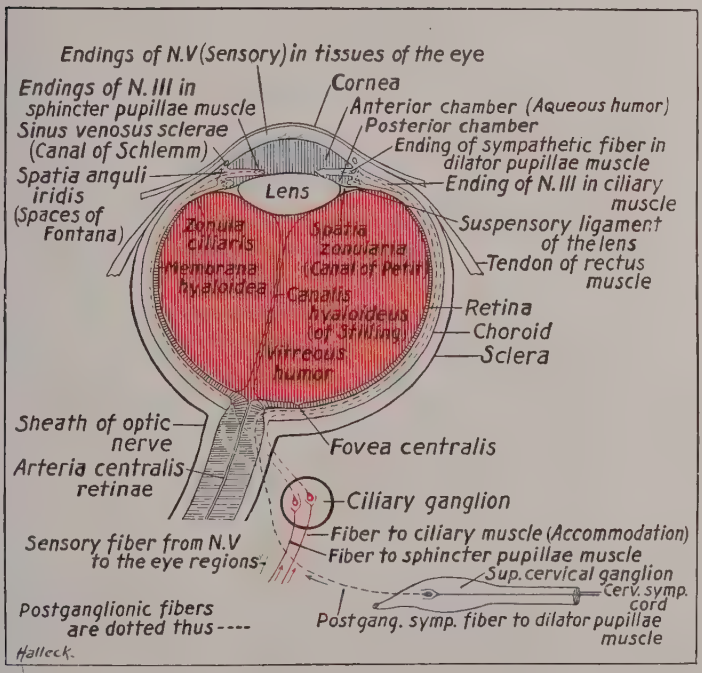

Endings of N.V (Sensory) in tissues of the eye
Endings of N. III in sphincter pupillae muscle
Cornea
Anterior chamber (Aqueous humor)
Posterior chamber
Sinus venosus sclerae (Canal of Schlemm)
Ending of sympathetic fiber in dilator pupillae muscle
Spatia anguli iridis (Spaces of Fontana)
Lens
Ending of N. III in ciliary muscle
Zonula ciliaris
Spatia zonularia (Canal of Petit)
Suspensory ligament of the lens
Membrana hyaloidea
Canalis hyaloideus (of Stilling)
Tendon of rectus muscle
Retina
Choroid
Vitreous humor
Sclera
Sheath of optic nerve
Fovea centralis
Arteria centralis retinae
Ciliary ganglion
Fiber to ciliary muscle (Accommodation)
Sensory fiber from N.V to the eye regions
Fiber to sphincter pupillae muscle
Sup. cervical ganglion
Cerv. symp. cord
Postganglionic fibers are dotted thus ----
Postgang. symp. fiber to dilator pupillae muscle
Halleck.

Fig. 79.—Diagrammatic representation of the structure and innervation of the eye. (From Jackson: *Experimental Pharmacology*, The C. V. Mosby Co.)

theory of accommodation for near vision is that a change in the shape of the lens is brought about indirectly through contraction of the ciliary muscle, which is innervated by the oculomotor nerve. This muscle lies between the choroid and sclerotic coats, attached to the scleral spur, and is composed of both circular and radial fibers. The circular fibers upon contraction act like a sphincter in decreasing the circumference of the ciliary ring. This pulls the ciliary process forward and loosens the tension of the fibers of the suspensory ligament on the capsule of the lens so that the anterior face of the lens bulges. The tension of the capsule is the important feature underlying this act and not mere elasticity of the lens substance. This is shown by the fact that if the capsule is pierced the semisolid lens substance is forced out as a blister, and if the capsule is entirely removed the lens does not return to its original shape after being deformed. Furthermore, the capsule is not uniform in thickness, the area at the anterior pole being thinnest, while the posterior face is relatively thick throughout. Thus during accommodation for near vision, when the lens assumes the shape imposed upon it by the capsule, there is a greater

Fig. 80.—Purkinje-Sanson images. *A*, eye accommodated for far vision; *B*, eye accommodated for near vision.

degree of bulging at the anterior pole than in other parts of the anterior surface of the lens. With increasing curvature of the lens the principal focus is, of course, shortened, and divergent rays, which before came to a focus behind the retina, now come to a focus on the retina, and the image is a point-for-point representation of the object.

This explanation, which is essentially that given by Helmholtz, has the support of two critical experiments: (1) It can be shown that if the points of needles are inserted through the sclera into the ciliary body of the eye of a cat, and if the animal is made to accommodate for near vision, the outer ends of the needles move backward. This means that the points have moved forward, and since they were embedded in the ciliary body this must also have moved forward. (2) That the lens does change its curvature and that this change is confined almost exclusively to the anterior surface is demonstrated by the so-called Purkinje-Sanson images.

A lighted candle is held in front and slightly to one side of the eye of the subject. The observer sees in the eye of the subject three images of the candle almost in a horizontal line, two larger ones (*a*, *b*) erect (Fig. 80) and a smaller one inverted (*c*). Three watch glasses may be used to represent the anterior surface of the cornea, and the anterior and

posterior surfaces of the lens. These watch glasses will give three reflections of a candle flame of the same character as the Purkinje-Sanson images. When the watch glasses are removed, one by one, it is seen that the small inverted image is that reflected from the glass representing the posterior surface of the lens, the large central image is that reflected from the glass representing the anterior surface of the lens, and the outer, large erect image is that from the glass representing the cornea. Bearing in mind the reflecting surface responsible for each of the three images, the experimenter requests the subject to accommodate first for far vision, then for near vision. It will be seen that the outer erect image (*a*) does not change at all; the small inverted image (*c*), only very slightly; but the middle erect image (*b*) becomes smaller and approaches the other erect image. The explanation is, of course, that the anterior surface of the lens has become more convex and has approached the cornea, that there is no change in the cornea, and little in the posterior surface of the lens.

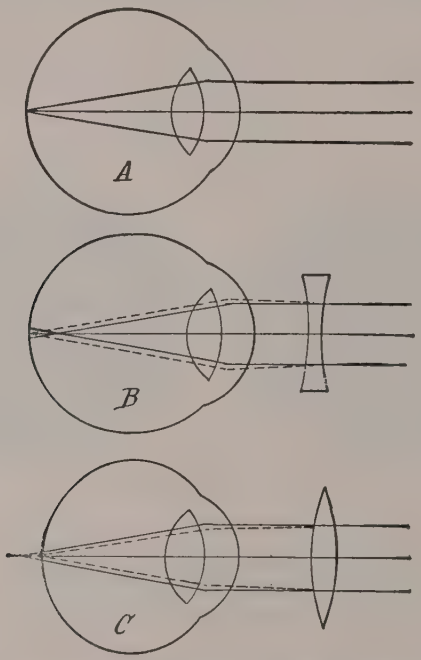


Fig. 81.—*A*, normal or emmetropic eye; *B*, myopic eye with correcting lens; *C*, hypermetropic eye with correcting lens.

Recently[36, 37, 40] there has been brought forward evidence that accommodation for far vision is accomplished not merely through relaxation of the circular fibers of the ciliary muscle, but that there is an accompanying active contraction of the radial fibers through the mediation of the sympathetic nervous system. It is now believed that contraction of these radial fibers increases the tension on the fibers of the suspensory ligament and aids in flattening the lens. The experimental proof is afforded by the finding that stimulation of the cervical sympathetic nerve in cats, dogs, and rabbits markedly increases the degree of farsightedness, i.e., flattening of the lens, even after the oculomotor nerve is cut or atropine has been applied to paralyze parasympathetic nerve

endings. Since stimulation of the oculomotor nerve produces nearsightedness, i.e., bulging of the anterior face of the lens, after cutting the cervical sympathetic nerve, it is most probable that accommodation for near and far vision involves the reciprocal action of both circular and radial fibers of the ciliary muscle, and the mediation of both parasympathetic and sympathetic nervous systems. The action of the muscle fibers controlling the lens would therefore afford an exact parallel with the behavior of the circular and radial fibers of the iris in the control of the pupil. A further evidence of this parallel lies in the fact that sudden startling stimuli, such as a noise or an electric shock, which have long been known to cause the pupil to dilate and to produce other effects of sympathetic nerve stimulation, also cause a momentary increase in farsightedness.

Common Defects in the Optical System of the Human Eye.—The ability to see distinctly objects near to the eye is therefore dependent on the fluidity of the lens. The lens hardens with age so that the elasticity of the capsule gradually ceases to be efficient in deforming it. Whereas a student of twenty years with normal eyes can see clearly at a distance of 10 cm., the *near point* of a person of forty is 22 cm., and for a person of sixty, 100 cm. This means that as one advances in years he has to hold his book farther and farther away. When this becomes awkward, recourse is had to spectacles composed of convex lenses which bring the near point to a more comfortable and convenient distance. The ophthalmologist considers a person with a near point of 28 cm. or more to be *presbyopic.*

Three other defects besides presbyopia or old-age farsightedness are commonly found in eyes.

1. *Myopia,* or *nearsightedness,* is often congenital, though it may be acquired. Either there is too great curvature in the lens or cornea, or much more commonly the eyeball is abnormally long. This is often the result of bulging in an anteroposterior direction on account of weakness in the coats of the eyeball, particularly the sclera. In such an eye the rays of light coming from a point on a distant object will come to a focus in front of the retina. Hence, when they finally reach the retina they will form a diffusion circle, and vision will be indistinct. To remedy this defect, concave lenses must be employed which will cause the rays to diverge before entering the eye, so that after passing through the lens they come to a focus on the retina (Fig. 81, *B*).

2. *Hypermetropia,* or *farsightedness,* may be due to abnormal curvature of the cornea or lens, or to defect in the shape of the eyeball. The latter is the more common type and is usually congenital. In the hypermetropic eye the light rays come to a focus behind the retina. The remedy in this case is use of convex lenses which cause the rays to converge to the right degree before entering the eye (Fig. 81, *C*).

3. A common defect which is of especial annoyance to readers is *astigmatism.* The astigmatic eye has the cornea or lens—usually the cornea—shaped more like the bowl of a spoon than a perfect sphere, that is, the radius of curvature is different in different planes. The radii in the vertical plane may be shorter than those in the horizontal plane. In this case the curvature is greater along the vertical meridian and the astigmatism is said to be "with the rule." "Against the rule" means that the horizontal meridian has the greater curva-

ture. The correcting lens in this case must be ground cylindrically so that rays coming along each meridian shall come to a focus at the same point (Fig. 82).

The size of the eyeball changes with the growth of the individual; in the babe the diameter is 17 mm., in the adult 23 to 24 mm. A difference in diameter means a difference in curvature as well as a difference in length of the eyeball. Since 1 mm. difference in diameter is equal to a refraction of 3 diopters,* this would mean that the child's eye might be hypermetropic to the extent of 21 diopters if the curvature of the cornea and lens were the same in the child as in the adult. But in the most extreme cases the hypermetropia of children seldom reaches 3 diopters. Therefore there must be compensation by increased curvature in the lens or cornea. That the cornea does not contribute toward this compensation is shown by the following ingenious experiment.

Gelatin was injected into the anterior chamber as this was drained of aqueous humor. Measurements of the outside face of the cornea were taken and the cornea then removed. The gelatin mold gave the curvature of the inner face. The ratio of the curvature of the

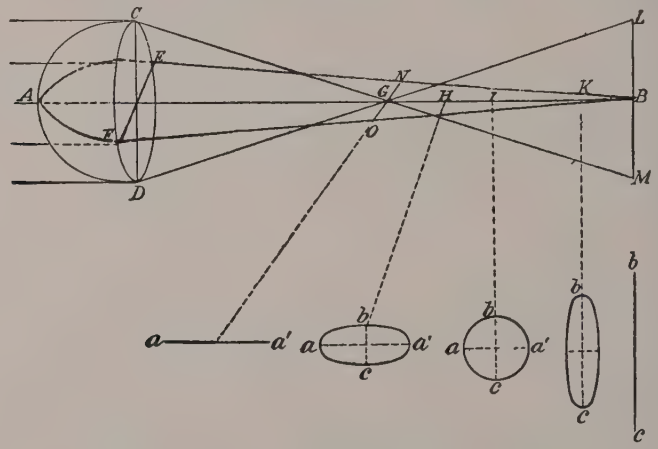


Fig. 82.—Images of horizontal and vertical lines at different foci in the astigmatic eye.

outside face of the cornea to that of the inner face was the same for a child of two months, a man of forty-four years, and a woman of seventy-six. The compensation must therefore occur in the lens. In the newborn babe the curvature of the anterior face of the lens has a diameter of 6 mm., and the posterior, 4 mm.; in the adult, the anterior face of the lens has a diameter of 8 to 9 mm., and the posterior, 6 mm. Therefore the lens of the child's eye is myopic compared with that of the adult, but the eyeball is hypermetropic. As the child grows there is reduction in the curvature of the lens, but a corresponding increase in the length of the eye-ball, so that the eye remains emmetropic,[40] or as nearly so as is possible under modern conditions of lighting in schools, constant reading. etc.

Corneal Ulcers.—The close relationship between the trigeminal nerve and the cornea has been known since the time of Magendie who showed that corneal ulcers follow injury to this nerve. Herpes of the cornea appears also to be due to disturbance at the peripheral fifth nerve endings. This "trophic" effect is now considered to be directly related to the

*One diopter = the curvature of a lens having principal focus 1 meter from the lens. The + sign is used if the focus is on the opposite side from the source of light as in a convex lens; the — sign is used if the apparent focus is on the same side as the source, as in a concave lens.

production of acetylcholine at these nerve endings. The normal cornea contains a considerable amount of acetylcholine, which is markedly reduced after cutting the trigeminal nerve, the degree of deficiency of acetylcholine paralleling the extent of corneal damage. Instillation of acetylcholine into the eyes of patients suffering from *keratitis neuroparalytica* has had strikingly beneficial results.

The Respiratory System of the Lens.—The lens of the eye consists of fibers arranged in concentric layers lying in a regular stellate, radial direction. Only the outer layers under the capsule have nuclei. The lens apparently grows throughout life and more and more fibers are constantly being laid down. Evidently the most central part of the lens represents the original embryonic tissue. Since the lens is some 3 or 4 mm. in thickness and has no blood supply though being bathed continually in aqueous humor, the question has been raised whether respiration goes on in the interior of the lens. The R. Q. (see page 733) of fresh lens substance proves to be 1, as if carbohydrate were being burned. The lens contains an auto-oxidizable system consisting of dialyzable glutathione and a thermostable protein residue. The sulfhydryl radical of glutathione can act as an H-donor, and when oxidized to disulfide can act as an H-acceptor. There is a marked increase in glutathione content of rat lens from birth to four months, after which it declines. By far the major change in glutathione content is in the lens cortex, not in its nucleus, and this argues in favor of the idea that the greater part of the respiratory activity of the lens takes place in its outer layers. Cataracts in laboratory animals, e.g., rats, are most conveniently produced by administration of naphthalene, or feeding a diet high in galactose. In galactose cataracts there is diminution in the ascorbic acid and glutathione content of the lens, the effect being again on the cortex, not the nucleus—at least in respect to glutathione. The glutathione content of fresh ox lens is decreased by exposure to ultraviolet light, and to a less degree by exposure to heat rays. It is suggested that this may have some bearing on the beginnings of the process which results in cataract. It is generally conceded, however, that heat, not ultraviolet light, is the cause of industrial cataract. Light denatures the lens protein and heat causes the coagulation. The effect is hastened by the presence of calcium which in old age may be present in higher concentration than in youth and therefore contribute to the formation of senile cataract.[6]

In general we may agree with Krause that in the production of cataract, mechanical injury is effective through precipitation of protein; heat is effective through its effect on enzyme action; naphthalene through removal of cystine, and diabetes through increase in organic acids. The relation of the various vitamins to cataract has still to be worked out, though, as has been mentioned, cataractous lenses contain less vitamin C than normal lenses.

Spherical and Chromatic Aberration.—In lenses made of glass we find several defects, two of which, spherical aberration and chromatic aberration, may be fairly well avoided by appropriate devices. In a biconvex lens like that of the eye, light rays passing near its edge are brought to a focus sooner than those passing through its center. When one set is in exact focus the other is not. In the microscope and camera we use iris diaphragms to allow only those rays to pass through the lens system which strike near its center. Exactly the same thing occurs in the eye. The iris screens off the light which would pass through the peripheral portions of the lens. The thicker the lens, the more the spherical aberration. Hence to be effective the iris should cover more of the lens during accommodation for near vision than during accommodation for far vision.

When rays of light of different wave lengths pass through a lens, the blue rays are refracted more strongly than the red and come to a focus sooner than the red rays. Therefore, the shorter rays of white light will be separated slightly from the longer rays upon passing through a lens, as well as through a prism, and the images formed by the lens will have fringes of color. In

optical instruments this defect is remedied by having lenses compounded of different kinds of glass. In the eye the defect is omnipresent but appears not to be too troublesome.

To demonstrate the presence of chromatic aberration in the human eye it is only necessary to look at the spectrum through a spectroscope. It is impossible to get a focus for the red and violet at the same time. If the eyepiece is adjusted so that the red is in focus, it is necessary to push it in to focus on the violet. This means that the normal eye is slightly myopic in violet light. In ordinary light the normal eye appears to focus principally for yellow green, the brightest part of the spectrum. Another means of demonstrating this phenomenon is to place a sheet of purple glass behind a screen pierced with a pinhole. Purple glass absorbs nearly all the middle of the spectrum, transmitting red and violet. The pinhole will appear as a red dot surrounded by a halo of violet if we accommodate for the red, and as a violet dot surrounded by a halo of red if we accommodate for the violet. An interesting experiment may be arranged to test the normal, the myopic, and hypermetropic eye; a word of a given number of letters is printed in red dots on a black background and another word of the same number of letters is printed over the first in blue dots. The emmetropic eye sees only a jumble of red and blue dots. The myopic eye reads the word in red, the hypermetropic the word in blue.

Visual Acuity.—Owing to chromatic aberration, acuity of vision, i.e., the power to see clearly or to discriminate detail in objects, is better for monochromatic light than for light having an extended spectrum. Visual acuity is defined by Hecht[20] as "the reciprocal of the visual angle which must separate two contours in order that they may be recognized as discrete." Visual acuity is measured as follows: two fine parallel lines or two points at a given distance are brought closer and closer together until the eye is just unable to distinguish that there are two and they fuse into one. The angle that these lines or points subtend at the eye under these conditions is called the *visual angle*. The reciprocal of the visual angle is the measure of visual acuity. It is claimed that better results are obtained if the test-object is a movable broken circle like the capital letter C. The subject of the test has to tell the direction in which the gap is pointing.[31]

For example, in a normal subject for a brightness of 20 millilamberts* a visual angle of 0.905′ was found; the visual acuity was, therefore, 1.105; for a brightness of 0.2 millilamberts, the visual angle of the same subject was 1.241′, the acuity, 0.806. In general, the visual angle is about 1 minute.† The tangent of an angle of $1' = \frac{1}{3438}$, therefore the details of an object whose distance from the eye is 3,438 times as great as its greatest diameter cannot be perceived by the average normal eye. For example, if the object is 2 kilometers away, the form, color, and detail within an area of 58 cm. diameter cannot be recognized. Yet for objects near at hand our visual acuity is remarkable. Most persons can see the width of the finest hair at arm's length, for the visual angle in this case is practically 1′. The width of the retinal image of the hair is 0.0049 mm., and this is practically the diameter of a single cone in the fovea. There is thus striking agreement between the size of the smallest retinal image and the diameter of macular cones, so that the theory is held that to see two separate objects their images must be far enough apart to include an unstimulated cone between them. Thus using the letter C as a test for visual acuity, the image of the tip above the gap falls on one cone, that of the lower tip on another cone, and the image of the gap itself falls on an intervening cone.

*1 lambert=light emitted by 0.07958 spherical candle power per square centimeter of a perfectly diffusing surface.

†In Robert Smith's *System of Compleat Opticks* (Cambridge, 1738) he says "Dr. Hook assures us that the sharpest eye cannot well distinguish any distance in the heavens, suppose a spot of the moon's body, or the distance of two stars, which subtend a less angle at the eye than half a minute; and that hardly one of a hundred men can distinguish it when it subtends a minute."

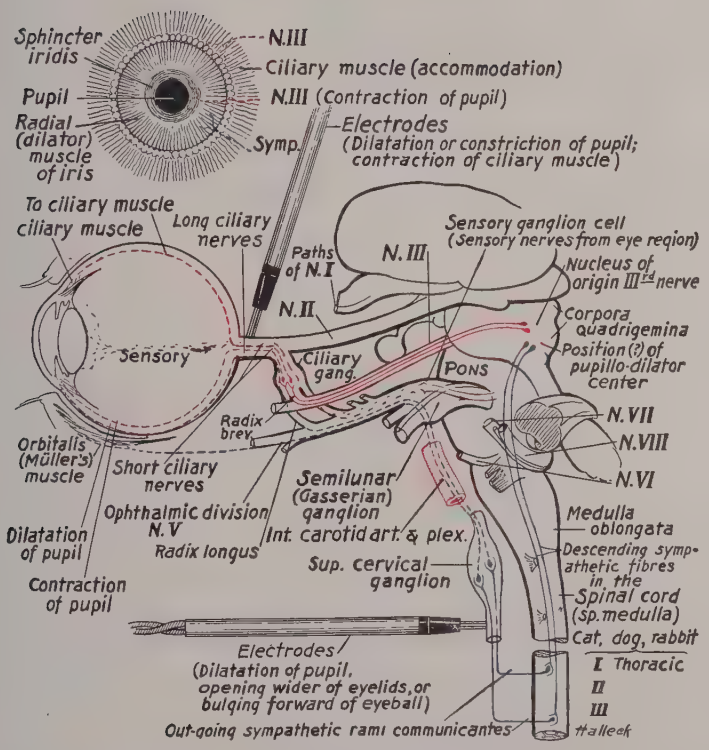


Fig. 83.—Schematic representation of the innervation of the eye. Postganglionic fibers are shown as broken lines. (From Jackson: *Experimental Pharmacology*, The C. V. Mosby Co.)

Visual acuity naturally depends upon the illumination of the test-object and also upon the contrast between the test-object and its background. There is a definite break at a visual acuity of 0.16, all values below this being mediated by the rods, those above by cones. With increasing illumination visual acuity increases slowly at first, then more rapidly, until finally at high intensities it becomes constant. To explain this phenomenon Hecht postulates that the retinal cones differ among themselves in their thresholds. Only a few cones are functioning at low intensities, and these are situated relatively far apart. With increasing illumination more and more cones are activated, and since visual acuity is dependent upon the number of cones in action, visual acuity will increase as the distance between the functional elements decreases. When all the cones are functioning, there will be no increase in visual acuity with further illumination. The curve relating the logarithm of the intensity of the light and visual acuity in normal individuals is S-shaped, the lower limb being obviously attributable to the action of the rods, and the remainder of the curve to the cones. In totally color-blind individuals—those whose retinas entirely lack cones—the curve relating light intensity and visual acuity is merely a continuation of the lower limb of the S and does not show the abrupt rise of the curve for the normal individual. In the night-blind person the rod portion of the curve should be lacking.[20]

There are serious difficulties in the way of proving the usually accepted theory that to see two separate objects their images on the retina must be far enough apart to lie on each side of an unstimulated cone, for it is almost impossible to hold the head and eyes still enough so that there is not a movement of at least 0.0049 mm. The eye, even during concentrated effort to keep it fixed, is found to move through an arc of 4′ at intervals of a second, and between these excursions there are fine oscillations in addition.[1] Furthermore, the area of the retina stimulated is greater than that subtended by the visual angle because of the spreading of light through irradiation.

Visual acuity is not the same for all shapes of objects. The ophthalmologist tests visual acuity by ability to read letters or characters on a chart which because of their size and distance from the eye subtend known visual angles. It is found that the capital letter *B* is most easily seen. If the visual acuity for *B* is taken as 100 per cent then for certain other letters the values are as follows: $L = 71$, $T = 74$, $O = 80$, $D = 82$, $Z = 84$, $R = 88$, $H = 92$.[40]

On account of the defects in the optical system of the eye, visual acuity is greatest when the pupil is fairly constricted, i.e., with a diameter of from 2 to 4 mm. It varies also in the normal eye not only with the intensity but also with the wave length of the light,[44] being greatest for monochromatic light nearer the end of the visible spectrum, i.e., for yellow light; it is only very slightly less for white and red light, about a third of this value for green light, and less than a fifth for blue light. The increase of visual acuity in monochromatic yellow light may be ascribed to the sharper focusing obtained by elimination of the blue rays, and a consequent increase in the definition of the retinal image by reducing the influence of chromatic aberration.

If different portions of the retina are tested, it is found that visual acuity diminishes abruptly when the light rays fall just outside the fovea, and falls off rapidly from the border of the fovea to the periphery. This is probably to be explained by the peculiar histological arrangements in the fovea (see page 262). Visual acuity diminishes with age; it lessens roughly one-tenth for every ten years between the ages of fifteen and sixty.

Visual acuity must be distinguished from aligning power. Visual acuity or resolving power is measured by the ability to distinguish two objects, aligning power is the ability to bring two marks into the same line, such as is required in reading a vernier scale, or a range finder. The least visual angle possible for aligning is $\frac{1}{6}$ that for resolving, and in many trained individuals the necessary angle is as low as 3″. Hartridge explains the fact that the aligning power of the eye is so much greater than its visual acuity by supposing that we actually take advantage of the imperfections of the optical system of the eye. The image of a point

source of light is not a point on the retina but a blur circle. A slight displacement of the image would affect the relative illumination of different cones, and if the retina were capable of detecting such differences, this would explain the extreme sensitivity of the eye in recognizing discontinuity in a line.[18]

Pupillary Changes.—The iris of the eye has been compared to the diaphragm of a camera or microscope for cutting off rays which would pass through the periphery of the lens. The analogy may be carried further. Just as we vary the size of the diaphragm opening in the camera, making it larger when photographing distant objects, and smaller for near objects, so in the act of accommodation the pupil is dilated for far vision, and constricted for near vision. The change in the size of the pupil is brought about by the action of the circular and radial smooth muscle fibers of the iris. The circular fibers are innervated by the third cranial nerve, and the radial fibers by nerve fibers from the cervical sympathetic.

The conditions under which the pupil in the body constricts are:

1. During accommodation for near vision, the "accommodation reflex."

2. When there is a sudden increase in light, the "light reflex." This is often absent in syphilitic patients. When the light reflex is absent, but the accommodation reflex is present, the condition is known as the Argyll Robertson pupil. The lesion lies either between the retinas and the anterior corpora quadrigemina, or between these bodies and the third cranial nerve.

3. Upon stimulation of the ciliary ganglion or of the ciliary nerves, or after cutting the cervical sympathetic nerve.

4. By the action of certain drugs, such as morphine and opium.

5. During severe pain.

6. In the earlier part of the third stage of anesthesia, i.e., after the corneal reflex has disappeared.

7. During sleep.

The pupil dilates under the following conditions:

1. During accommodation for far vision.

2. Sudden diminution of light.

3. Stimulation of the cervical sympathetic nerve or after cutting the third cranial nerve.

4. By the action of certain drugs, such as atropine, adrenalin.*

5. In fear.

6. In the second stage of anesthesia, i.e., between loss of consciousness and loss of the corneal reflex, and again toward the end of the third stage and in the fourth stage.

Under natural conditions the pupil is most widely dilated in the dark, i.e., when the eye is dark-adapted, and most constricted in bright light, i.e., when the eye is light-adapted. The range in the normal eye is from a diameter of 8 mm. to 1 mm. Light falling on or being withdrawn from one eye affects the other, so that even if one optic nerve is atrophied light falling on the

*Subcutaneous injection of adrenalin into man or dropping it into the eye does not under normal circumstances cause dilatation of the pupil. The pupil dilates only if there is glaucoma. This constitutes the Knapp test for glaucoma.

functional eye causes constriction of the pupil of the blind eye. The change with increasing brightness of the light is shown in Table III.

TABLE III

BRIGHTNESS IN MILLILAMBERTS	DIAMETER OF PUPIL IN MM. BOTH EYES OPEN	DIAMETER OF PUPIL IN MM. ONE EYE CLOSED
0.0	7.4	7.5
0.00015	7.15	7.25
0.60	5.3	6.5
6.3	4.1	5.7
126.0	2.6	3.3
2000.0	2.0	2.0

The rate at which the dilated pupil of the dark-adapted eye closes when suddenly illuminated, and the rate at which the constricted pupil of the light-adapted eye opens when the light is withdrawn are given in Table IV. The figures given are the average results obtained on six normal persons by use of the cinematograph camera.

TABLE IV

CLOSING OF PUPIL		OPENING OF PUPIL	
TIME IN SECONDS	DIAMETER IN MM.	TIME IN SECONDS	DIAMETER IN MM.
0.0	8.	0	2.9
0.5	6.4	1	3.5
1.0	5.3	3	4.7
1.5	4.4	5	5.6
2.0	3.9	15	6.6
2.5	3.5	29	6.9
3.0	3.3	60	7.3
3.5	3.2	180	7.6
4.0	3.2	300	7.6
4.5	3.1		
300.0	3.1		

The circular fibers of the iris, whose contraction causes constriction of the pupil, evidently work much faster than the radial fibers, which cause dilatation. The pupil closes nearly to its minimum diameter in three seconds, while as many minutes are necessary for a maximal opening.[43] There is, however, a reciprocal arrangement in the innervation of these antagonistic muscle fibers, since stimulation of that part of the motor cortex having to do with the eye causes dilatation of the pupil after the cervical sympathetic nerve has been cut. Furthermore, it has been shown by infrared photography that dilation of the pupil of the normal eye during dark adaptation is partly the result of the passive pull of the iris tissue and partly the result of contraction of the dilator fibers. If the sympathetic has been cut, dilation after dark adaptation is only two-thirds the maximal and the size of the pupil is determined by the balance between the elastic pull of the iris tissues and what has been termed "residual tone" of the sphincter. If both the sympathetic and oculomotor nerves are cut, the pupil remains fixed at slightly more than two-thirds the maximal diameter. In this case the "residual tone" of the sphincter has been abolished and the pupillary size is determined solely by the pull of the iris tissue. If the oculomotor nerve alone is cut, the pupil is fixed at its maximum diameter, and the relaxation of the relatively feeble radial fibers during light adaptation is too slight appreciably to affect the size of the pupil.

The change of the pupil to intensity of light, or the light reflex, appears to dominate the accommodation reflex, since the change during the accommodation reflex when the eye is light-adapted, i.e., out of doors, is quite different from that when the eye is adapted for dim light or in a slightly darkened room. Immediately upon increasing the intensity of the light there is a response; but although accommodation begins for an object just under twenty feet away and increases the nearer the object approaches the eyes, apparently it is not until the object is only a foot away that the pupil begins to constrict.

Associated with the accommodation reflex when an object is viewed at close range is the convergence reflex by which the two eyes are turned in towards the nose through contraction of the internal recti and simultaneous relaxation of the external recti of each eye. Here the accommodation reflex is the stronger since a considerable degree of near accommodation can be obtained by interposition of spherical lenses without convergence, whereas the reverse experiment with interposition of prismatic lenses shows that convergence is always accompanied by a slight change in accommodation.[35]

Although the pupil is normally controlled reflexly through sympathetic and parasympathetic nerves, the iris in an excised eye responds locally to a spot of light. Both the iris of an excised eye and the isolated iris respond to those drugs which in the normal eye cause pupillary changes. For example, acetylcholine, a parasympathomimetic drug, acts on the circular fibers but does not affect relaxed dilator fibers; whereas sympathomimetic drugs, as epinephrine, act on the dilator fibers. Atropine, however, which is generally considered to paralyze parasympathetic nerve endings, not only causes relaxation of the sphincter but of the dilator fibers as well, provided the latter are in the contracted state after application of epinephrine.

Retinoscopy.—For the examination of the interior of the living eye an instrument invented by Babbage in 1848 and rediscovered by Helmholtz in 1851, the *ophthalmoscope,* is usually employed.* It is said that the invention of this instrument was as important for ophthalmology as the stethoscope for medicine. The pupil of the eye is dark, and the reason for this is that rays of light which might illuminate the interior of the eyeball are reflected practically straight back in the direction of their source because of the narrow opening of the pupil. Hence, the observer shuts off his own light, and looking into the subject's eye is like looking into a darkened room through a small opening. The ophthalmoscope is composed of a mirror, either plane or concave, with a hole in its center. Light is reflected from the mirror into the subject's eye and the interior of the eye which is now illuminated is viewed through the hole in the mirror. Two methods of using the ophthalmoscope are in vogue. In the *direct method* the observer's eye is held close to the subject's eye and both observer and subject accommodate for far vision. An erect virtual image of the fundus of the eye will be seen about twelve times natural size. In the *indirect method* the observer stands about two feet in front of the subject, and interposes between the ophthalmoscope and the subject's eye a biconvex lens of about 6 cm. focal length (Fig. 84). Both the subject and observer focus on the same intermediate plane. The image seen in the indirect method is real, inverted, aerial, and magnified only some three times, but has the advantage that a larger field is seen than in the direct method. The optic disc and the retinal blood vessels are the landmarks

*A translation into English of Helmholtz' original essay of 1851, together with reproductions of his drawings of the ophthalmoscope, is now available in the Am. Jour. Physiol. Optics, II, p. 121.

to be noted. The degree of myopia and hypermetropia in defective eyes can be determined by the use of the ophthalmoscope. In the myopic eye the rays are convergent as they leave the eye. Hence for the emmetropic eye of the observer to see the fundus clearly a biconcave lens must be placed before it to correct the convergence of the rays. Similarly the emergent rays from the hypermetropic eye diverge, and a convex lens must be placed before the observer's eye to see the fundus clearly.

The term "ophthalmoscope" has come to be associated with an instrument which has, in addition to the mirror with a hole in its center, a disc with a series of lenses so arranged that they can be brought into position behind the aperture and indicate this correction for an abnormal eye.

The modern ophthalmologist, however, uses the original ophthalmoscope as described by Helmholtz (i.e., a plane circular mirror having a small portion in its center unsilvered or having an actual hole in its center and now termed a retinoscope) in quite a different manner for eye testing. The procedure is known as *skiascopy* or skiametry, meaning a viewing or measuring of shadows. Light is projected into the subject's eye from a small source, and the observer's eye sees the lighted area through the hole in the mirror. But the light rays reflected from the subject's retina pass through apertures in three screens: the iris of the subject's eye, the retinoscope, and the iris of the observer's eye. If the observer's

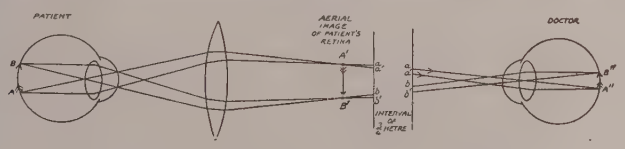


Fig. 84.—Indirect method of use of ophthalmoscope.

eye and the subject's eye are both emmetropic and both are accommodated for far vision, and the observer is at the far point, i.e., 6 meters away, then the whole pupil of the subject's eye appears ablaze with light. But if the observer is at some other distance, or there is some accommodation for near vision, or either the observer's or the subject's eye is myopic or hypermetropic, then a dark shadow cuts a segment out of the bright disc of light in the subject's pupil like a partial eclipse of the sun, and if the mirror is rotated about its vertical axis this shadow moves across the pupil in the same direction as the rotating mirror. If the observer is nearer than the far point, the shadow rotates in the opposite direction to the mirror. Since for the normal eye the far point may be taken as exactly 6 meters, the degree of myopia or hypermetropia of the subject's eye can be found by comparing his far point, i.e., the distance at which there is no shadow in his pupil, with the normal; or the observations may be made at the normal far point and lenses interposed before the test eye until the far point is normal. In the latter method the movement of the shadow in the same direction as the movement of the mirror indicates that hypermetropic correction is necessary (Fig. 85); movement in the opposite direction signifies myopia (Fig. 86). In actual practice, however, 6 meters are too great a distance for accurate observation of the movement of the shadow. Generally, the oculist places himself a meter away from the subject and interposes a lens of plus 1 diopter in front of the subject's eye so that the relaxed eye now focuses on a point 1 meter

in front. The oculist then adds the necessary lens to throw the focus of this artificially myopic eye back to infinity, or rather, 6 meters. The strength of the lens to use for the subject's glasses is, of course, the value of the second lens minus 1 diopter. If the oculist places himself at some other distance than 1 meter, a corresponding change must be made in the strength of the first lens.

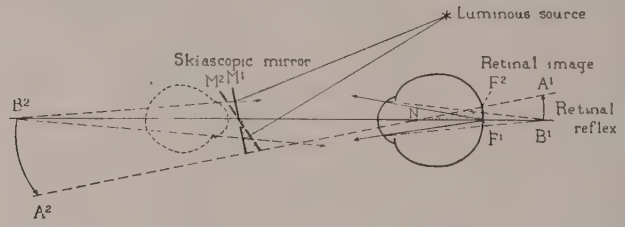


Fig. 85.—Objective skiametry. Hypermetropic eye. Light is reflected from mirror $M,^1$ into subject's eye. Because the eyeball is too short, the image appears to lie at $B.^1$ B^2 is the image in the observer's eye. When the mirror is rotated to the position $M,^2$ the shadow represented by the stippled area, moves to A^1 in the same direction as the mirror.

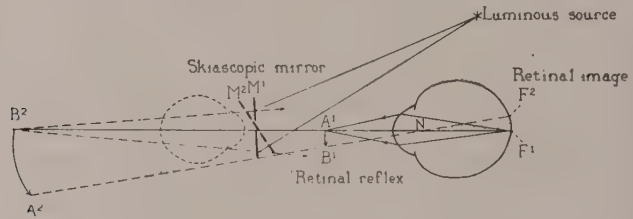


Fig. 86.—Objective skiametry. Myopic eye. The shadow moves in a direction opposite to that of the mirror.

Intraocular Pressure.—One other factor is necessary in maintaining a perfect optical system in the eye, namely, constancy of intraocular pressure. The fact that a small cut made in the cornea causes the aqueous humor to drip at a constant rate has been taken as proof that aqueous humor flows continuously through the anterior chamber. But normal aqueous humor contains only 0.02 per cent of protein, and the longer the fluid is allowed to flow from this cut the more nearly it approaches normal blood serum, which has a protein content of 7 per cent. The chief evidence for the constant circulation of aqueous humor is that particles, such as those of India ink, injected into the anterior chamber of the rabbit's eye collect in the corners at the so-called filtration angle. The rate of production of aqueous humor is fairly slow since it takes about an hour to renew the fluid in the anterior chamber. It is generally considered that there are three ways of exit for the aqueous humor: (a) at the filtration angle it may pass through the spaces of Fontana into the canal of Schlemm and thence to the ciliary veins—by far the greater part of the fluid leaves by this channel; (b) a small quantity, not more than 2 per cent, passes between the suspensory ligaments and reaches the posterior surface of the lens to nourish the vitreous humor; it passes to the posterior of the eyeball by means of the hyaloid canal (the lymph space which originally surrounded the fetal

Fig. 87.—Normal fundus, left eye, showing optic nerve, retina, and retinal vessels. (From Parkinson: *Ear, Eye, Nose and Throat Manual for Nurses,* The C. V. Mosby Co.)

hyaloid artery and which persists after the latter disappears), and leaves the eyeball with the optic nerve; (c) some also passes through the anterior surface of the iris into the veins of that structure.

The intraocular pressure under normal conditions is found to be 25 mm. of mercury. Now if the rate of flow of the aqueous humor were suddenly increased or diminished, the cornea might be forced out, or the eyeball might become wrinkled. This would derange the optical system and the image on the retina would be distorted. Consequently, there should be some arrangement by which the intraocular pressure can be maintained fairly constant. Henderson and Starling showed that intraocular pressure varies with blood pressure, but the changes in intraocular pressure lie within comparatively narrow limits. Thus, if the arterial pressure is raised from 70 to 180 mm., the intraocular pressure rises only from 23 to 40 mm., provided the conditions of osmotic pressure of the blood and aqueous humor remain unchanged. The question whether the aqueous humor is the result of a true secretory process or of simple dialysis has now been settled in favor of the former point of view. The osmotic pressure of this humor is markedly modified by the anesthetic used; if the animal is under amytal, or a local anesthetic is used, the aqueous humor has an osmotic pressure equal to 0.004 M NaCl greater than that of the corresponding serum, hence the inference that this humor is a true secretion rather than a mere dialysate.

CHAPTER XXIII

PHYSIOLOGY OF THE RETINA

Once the light rays have passed through the various refractory media of the eye and reach the retina, there is a change from a disturbance which has been travelling at the rate of 180 thousand miles per second, to one which passes at the rate of some 300 feet per second. The radiant energy of the light sets up a reaction in the retina which initiates a series of nerve impulses and when these reach the brain there is experienced a sensation, and the person "sees."

The Layer of the Retina Stimulated by Light.—The retina possesses three layers of neurons. The light first strikes the fibers from the ganglion cells, then passing through these, reaches an intermediate layer of bipolar cells, and finally impinges upon the rod and cone cells. Beyond the rods and cones lies a layer of flattened pigment cells.

If we trace the ray of light into the eye from an object upon which we are fixing our gaze, we find that it falls upon a specialized part of the retina. This region, *the macula lutea or yellow spot,* is about 0.6 mm. in diameter, and its center is a depression, the fovea centralis. In the fovea only cones, no rods, are found,* and the depression is caused by the thinning out of the layers of the retina, so that at this point the light impinges almost directly on the cones without having to pass through the several layers of the retina, as it does elsewhere. Both rods and cones are present beyond the fovea. The number of rods increases for a distance of 5-6 mm. beyond the fovea, then diminishes further out. The upper and nasal quadrants of the retina are better supplied with rods than the lower and temporal quadrants.[39] Each optic nerve is estimated to have 400,000 fibers and each retina 7,000,000 cones and 125,000,000 rods. In the fovea each cone cell has, as it were, a "private line" to the brain, one ganglion cell and its axon serving one cone with, however, possibility of interaction between neighboring receptors; but in the outer parts of the retina there may be as many as 10 cone cells to 1 ganglion cell, and 250 rod cells to 1 ganglion cell.[30]

The question arises, which of the three neurons act as the specialized receptors for radiant energy, the ganglion cell and its axon, the bipolar cell, or the rods and cones? It cannot be the ganglion cells or their fibers, since the optic disc, the place of exit of the optic fibers from the retina, is insensitive to light, the so-called *blind spot of vision.* If the reader closes his left eye, and holding the book about ten inches away, looks at the cross in Fig. 88 with his right eye, the circle will be invisible. The optic disc lies to the nasal side of the fovea centralis in each eye. Since the light rays cross inside the eye before they reach the retina, the gap in our field of vision lies on the temporal side, or to the right, for the right eye.

An important thing to note is that no sensation is aroused when light impinges upon the blind spot; in other words, there is blankness, not blackness. This shows that blackness is not due to absence of stimulation, as some investigators have thought. The reason we are

*Histological examination shows that the structure of a foveal cone is somewhat intermediate between a typical cone and a typical rod. The number of cones in the densest portion of the fovea is approximately 150,000 per sq. mm.

not conscious of our blind spots is that they fall in different parts of the visual fields of each eye; that is, the deficiency in one eye is made up in the other. To show the existence of the blind spots in both eyes simultaneously, it is necessary to separate the two fields of vision so that they do not overlap. This can be done by holding a screen vertically between the eyes so that the visual field seen by each eye extends only to the midline.

More positive information as to the location in the retina of the receptor organs is afforded by looking at a dull cloudless sky, or at a colorless gray or white screen; flashes of light like sparks are seen. If these are watched carefully, they are found not to be moving in a hit-or-miss fashion, but to follow definite paths. Whether these are the shadows of leucocytes or erythrocytes is still a matter of dispute. Because of their numbers it seems more likely that they are caused by erythrocytes passing through capillaries in the inner nuclear layer of the retina.

This effect must be distinguished from the "muscae volitantes" (flying flies), motes which appear to float steadily downward when the gaze is directed upward. These motes are caused by small particles in the vitreous humor. If one attempts to focus upon them, they fall faster than the eye moves so that they seldom interfere with direct vision. The appearance of these motes has attracted the attention of the physicist Michelson, who finds that when properly viewed, their pattern is one of concentric circular fringes like Newton's rings, with a bright inner border of red, and a dark outer border of blue. This is a typical diffraction pattern.[33]

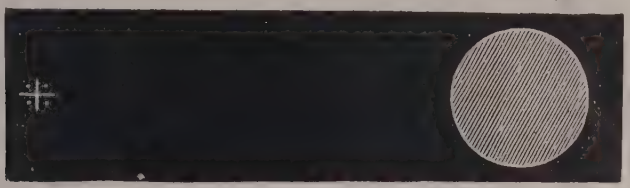


Fig. 88.—To demonstrate the blind spot, close the left eye, hold the page ten inches from the right eye and look at the cross. The circle will be invisible.

When a strong light is thrown on the side of the eyeball, shadows of the blood vessels lying in front of the retina appear as tortuous dark lines on a light background and are known as Purkinje's figures. If the eye is kept motionless and the position of the source of light and the position on the screen of Purkinje's figures are noted, then upon moving the light to a new position, it is found that Purkinje's figures also shift their position, but to a much less extent. From the data of this experiment the distance back of the blood vessels at which the light is exerting its effect can be calculated. This proves to be from 0.2 to 0.3 mm. Histological examination of the retina shows that this is approximately the distance of the rods and cones from the blood vessels.

The Demonstrable Changes Taking Place in the Retina Upon Stimulation.—For vertebrates in general including man, these are (1) action currents and (2) bleaching of the visual purple, and for the lower vertebrates (3) movements in the rod and cone cells and (4) migration of pigment in addition.

1. In a skeletal muscle the action current during a single contraction follows very closely the scheme outlined in Fig. 17 (page 25). If one end of the muscle is injured, this injured end is found to be permanently electronegative to the uninjured part, and a galvanometer connecting these two points shows

a permanent deflection. This is the current of injury. When the muscle contracts there is a momentary return of the galvanometer needle to zero when the so-called wave of electronegativity passes by the lead from the uninjured part of the muscle. This is known as the negative variation or action current. If one lead to a galvanometer is connected to the cornea of an excised eye of a frog or rabbit, and the other to the posterior part of the eyeball or to the optic nerve, there is a similar current with the cornea as the positive pole. But the earlier investigators on this subject found that when the eye was stimulated by a beam of light, instead of a negative variation and a return of the galvanometer needle to zero, there was an increase in the same direction as the current at the moment the light was turned on, and again when it was turned off. Retinal action currents are therefore much more complicated than muscle action currents. They are a complex of negative potentials (probably associated with excitation) and slow positive potentials (probably associated with inhibition). The locus of action is in the synaptic layers of the retina, i.e., proximal to the rods and cones.[15] Colored lights as well as white light produced this effect, yellow light giving a greater effect than violet. Recent experiments with more

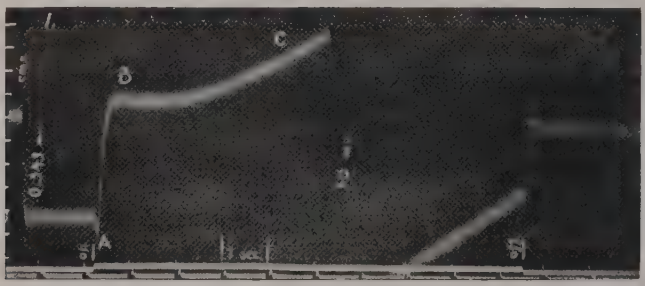


Fig. 89.—Photoelectric current of excised frog's eye. Leads cornea-fundus. Light of intensity of 43.2 candle power thrown into eye at "on," off at "off." A= negative variation, B=action of cones, C=action of rods. (From Hartline: Am. J. Physiol. 73: 600, 1925.)

delicate instruments show that there is a very slight negative variation immediately preceding the rapid increase in negative potential (Fig. 89) if one electrode is placed on the cornea.

The photoelectric currents are shown to a better advantage if the excised eye is cut in two and the posterior half used. In this case one electrode touches the retina, the other the optic nerve.[5] But it is also possible to record photoelectric currents in the intact animal, one electrode being connected to the cornea of one eye, the other to the cornea of the other eye or to any other part of the body. Two methods have been employed in experiments with the human eye. In one method a pair of goggles is fitted to the face with a watertight seal. The subject lies on his back, saline is introduced into each chamber of the goggles, and leads connect the conjunctiva of each eye to the galvanometer. The eye is suddenly illuminated and the action current recorded. The action currents caused by the wink reflex and other movements of the lids or of the eyeball, interfere with a clear demonstration of the photoelectric current due to illumination of the retina, and for this reason the second method in which the conjunctiva is anesthetized with holocaine is preferable. One electrode is placed directly on the cornea of one eye, and the other electrode is held in the month. The small negative variation has been called the a-wave; the first sharp rise which is positive, the b-wave; and the succeeding longer slow rise, also positive, the c-wave. The a-wave is more marked in the light-adapted eye than in the dark-adapted eye; the height of the b-wave varies with the intensity of the illumination; the c-wave appears only when the

illumination is high and may be entirely absent under all conditions in certain mammals, for example, the rat. Upon cessation of illumination there is again a latent period, followed by another positive rise, the *d*-wave, the "off-effect." Because light anesthesia abolishes the *c*-wave first, Granit has designated the process underlying the appearance of this wave as PI; Bartley ascribes it to action in the ganglion cells. Under deeper anesthesia the *b*-wave disappears; Granit designates the processes underlying it at PII, and Bartley ascribes it to action in the bipolar cells. Finally, since under deep anesthesia only the *a*-wave is left, Granit calls the process underlying this wave PIII, and Bartley considers it to be the result of activity in the rods and cones. The *d*-wave, the "off-effect" which Granit associates with PIII, is of particular interest since here removal of a stimulus is the source of excitation. This cannot be merely a peripheral affair, i.e., in the eye alone, since it can be registered from leads from the occipital cortex of the cerebrum. That certain sense organs do respond only to cessation of a stimulus has been clearly shown by Hartline for the eye of the mollusk, pecten. In this animal there are two layers of visual cells; action currents appear in the optic nerve fibers from the proximal layer of visual cells only during illumination, and from the distal layer only upon reduction or cessation of illumination.

A general law has been formulated by Weber to show the relation between strength of (external) stimulus and intensity of (subjective) stimulation; the just appreciable increase of stimulus bears a constant ratio to the original stimulus. Thus, if one can just perceive a difference between a 10 Gm. weight and an 11 Gm. weight when placed on the palm of the hand, the ratio is 1/10. Therefore, no difference will be felt between a weight of 100 Gm. and 105 Gm., or between 200 Gm. and 210 Gm.; $\frac{1}{10}$ the weight must be added in each case to be able to appreciate a difference.

This can be expressed as a differential equation which upon integration becomes

$$S = k \log 1 + c$$

where S = the measure of sensation, 1 = the measure of the stimulus, k = a constant, and c = a constant of integration. Expressed in this form it becomes the Weber-Fechner law: the sensation is proportional to the logarithm of the intensity of the stimulus.

Comparison of (objective) retinal currents evoked by illumination, with the (subjective) sensations in man evoked by similar excitation suggests that these two phenomena are merely different aspects of the same retinal response.[26] Therefore, we should expect that all the retinal currents, even in excised eyes, would show a relation to the intensity of the stimulus according to the Weber-Fechner law. We do find that for a limited range the height of the action current curves varies with the intensity of the light.

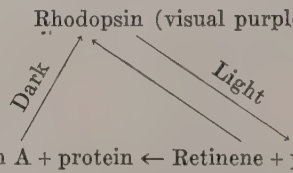
For very strong or very weak illuminations the law does not hold. For weak illumination the action current varies as the square root of the intensity. No simple law, therefore, applies to the whole range of the curves. From Fig. 89 it will be seen that there are two prominent maxima—the B- and C-waves. The time from the beginning of the response to each of these maxima is independent of both the intensity and the duration of the stimulus, 0.27 sec. to the first, 0.70 sec. to the second. In addition to these two maxima there are often a third and fourth. The first rather sharp maximum is attributed to the action of the cones, the second, more slowly rising maximum, to that of the rods. The cause of the third and fourth maxima is unknown.[5]

2. *Visual purple* (found only in the rods) is bleached by the action of light. If the eye of a rabbit previously kept in the dark is exposed under proper conditions to light coming through a window, it is found that the parts of the retina upon which the light has fallen are colorless, while those parts

shaded by the window bars retain their red purple color. Rhodopsin, or visual purple, may be extracted from freshly excised eyes. Such a solution is bleached by light according to the kinetics of a monomolecular reaction. The temperature coefficient of this reaction is 1 over a range of 30° C. This indicates that the reaction is a simple one and of a real chemical nature, not a physical one, such as diffusion. In the visual process, therefore, the first step in the response of the rods consists in the photochemical decomposition of visual purple. If the reaction in the vertebrate eye follows the same process as that shown by Hecht[19] to take first place in the photosensitive substances in certain mollusks, this first reaction results in the production of catalyzers which control the velocity of a second chemical reaction, and this in turn initiates the nerve impulses.

According to Lythgoe, the bleaching of visual purple occurs in several steps: first, "transient orange," a substance little affected by changes in hydrion concentration, is formed; this unstable product is converted thermally to "indicator yellow"; the result of further bleaching is the formation of colorless substances. During dark adaptation in the normal eye there is regeneration of visual purple, the kinetics of which reaction indicate that only a single substance is involved. One would expect that the process would demand the interaction of at least two molecules. The discrepancy between theory and fact may be explained on the ground that there is actually more than one chemical substance involved, but that one substance is in great excess of the other, and so influences the course of resynthesis.

The chemical reactions taking place during bleaching of visual purple involve vitamin A. This vitamin has for some time been associated with vision, for it has been found that animals deprived of vitamin A become night-blind, i.e., the rods do not function properly because of failure to synthesize visual purple. Light acting upon visual purple liberates a carotenoid, retinene, and this by a further reaction is converted into vitamin A. These products are yellow or colorless, and this explains the bleaching action of light. Vitamin A, therefore, is to be found mainly in the dark-adapted retina. The process is reversible, for retinene and vitamin A unite with a colloidal component, a protein of high molecular weight (above 200,000) in the restoration of visual purple. The light-adapted eye, therefore, contains only a trace of vitamin A. The vitamin is used up in these processes and must be continually furnished from the diet. This has been schematically pictured by Wald thus:



Since deficiency in vitamin A is so closely paralleled by failure to resynthesize visual purple, the standard method for determining vitamin A deficiency in both man and animals is to follow the course of the return of sensitivity during dark adaptation after previous exposure to light. For precise measurements an artificial pupil must be employed, and, although the most rapid changes occur in the first ten minutes, the curve should be followed for a full thirty minutes, since it is the latter part of this curve which is most affected by lack of vitamin A. In human experiments on withholding vitamin A from the diet,

it has been found that on the thirty-fifth day the minimum threshold for cones may be 3.4 times the normal, and that for rods 9.1 times the normal. Some observers have reported striking immediate results of administration of β-carotene under these conditions, viz., the restoration of normal thresholds of sensitivity in less than one hour.

It would seem that there should be some correlation between the different waves of the retinograph and the chemical phenomena occurring during the bleaching of visual purple and its resynthesis. Granit, however, finds no such correlation. On the contrary, he is of the opinion that only a small fraction of the visual purple, viz., that which occurs in the surface film of a rod, not the larger store within, is needful for excitation. The rise in sensitivity during dark adaptation would therefore not be a simple function of the curve showing the course of visual purple regeneration, and the rods might be forced to nearly maximal activity without incurring measurable losses in visual purple content.

The photosensitive substance in the cones has recently been isolated as "iodopsin" or "visual violet," with maximum absorption in the yellow. The suggestion is made that it, like "rhodopsin," is a conjugated carotenoid protein.

In the lower vertebrates (1) the cones shorten on exposure to light—there is some evidence that the rods lengthen also—and (2) the pigment migrates forward to surround the rods and cones, which carries with it the suggestion of retinomotor fibers. Such protection is evidently replaced in mammals by rapid pupillary movements.

Cone Vision and Rod Vision.—A difference in the functions of the rods and cones has been implied in the preceding paragraphs. Since the fovea possesses cones only and the number of cones diminishes and the number of the rods increases from the fovea to the periphery of the retina, we should expect to find differences in vision according to the place on the retina on which the light rays fall. A very simple method of charting the visual field is known as the hand or confrontation test.

The observer and subject stand at arm's length from each other. One eye of the subject is covered, e. g., the left, and the observer closes his own opposite eye, i. e., the right. The subject and observer look directly into each other's open eye. The observer then holds some small object, e. g., a pencil, in his left hand midway between himself and the subject as far out to his left as possible. The subject is instructed to announce the exact moment when he can see the moving pencil as it is moved in toward him. If the observer has normal eye fields he can easily discover whether the subject's fields coincide with his own.

Any shrinkage in the field can be mapped out on prepared charts. If there are scotomas, or the optic nerve is injured, there will be disturbances in one field. If there is pressure on the optic chiasma as in the case of pituitary tumor, the temporal side of each visual field will be lacking (heteronymous hemianopsia). If one optic tract is involved the temporal side of one field and the nasal side of the other will be lacking (homonymous hemianopsia). If there are lesions in the optic radiation, there may be complete homonymous hemianopsia or homonymous notching, depending upon the extent of the lesion. More accurate results are possible by using instruments, such as the perimeter, or the Bjerrum screen, designed for mapping central vision out to 30°.

Perimetric measurements show that distinctness of vision and appreciation of color are much greater in the fovea than toward the periphery.

It is generally stated that green is perceived only for a relatively short distance beyond the fovea, that sensations of red cease a little further out than

the green, sensations of blue and yellow persist for a region considerably beyond that for the red, but that at the periphery there is only a sensation of gray. The so-called color fields then are, roughly, concentric circles whose circumferences from the fovea outward represent the limits of green, red, blue, yellow and finally, gray. This observation was the origin of the "duplicity theory"; namely, that the cones subserve light and color perceptions, while the rods are concerned with perception of light but are incapable of initiating color sensations. The idea that the periphery of the retina is blind to color has taken firm root in the scientific literature on color perception, but too many reliable investigators have shown that the far periphery is not blind to colors, to leave room for doubt on this point. It is quite true, however, that a stimulus of strong intensity is required to produce the effect[46] and that the field for green is always narrower than that for white or gray.[42] It is found that the intensity of light necessary to produce color vision varies greatly from center to periphery of the retina, from meridian to meridian, and from one point to another along a single meridian. Furthermore, these variations appear to be individual rather than general. In the ordinary clinical practice of perimetry, colors of widely different intensity are used. For this reason the color fields appear limited. If the stimuli are strong enough the fields for white, red, blue and yellow are the same; green only appears not to extend to the periphery. If stimuli of equal or of the same order of intensity are used, the limits for red, blue, and yellow interlace or crisscross due to the difference in sensitivity in the different meridians.

In all justice, however, a word must be said in favor of the procedure of mapping out the color fields by perimetrical examination. If the colors of the same hue and intensity are always used for the tests and these have been carefully charted for the normal eye, departures from the normal may be very significant, particularly the changes in perception of the central colors at a narrow visual angle. In comparing retinoscopy with perimetry one author states, "The color fields and color changes furnish a more delicate test in the earlier stages of disease and at times furnish a clue to the seat of the trouble before an appreciable change has taken place in the form field."[34]

In addition to the difference in sensitivity of the fovea and periphery of the retina to color, there is also evidence of a difference in sensitivity to the intensity of the incident light.

There is a small star, Alcor, just above the large star, Mizar, at the bend of the handle of the Great Dipper. This small star is usually invisible when the gaze is concentrated upon it, i.e., for foveal or cone vision, but it comes into view when the gaze is shifted slightly and the rods are affected—the eye, of course, being dark-adapted.

The practical usefulness of the human eye is dependent upon *the sensitivity and range of response of the retina* to the stimulus of light in its various forms. The eye is found to operate under an enormous range, 20 billion to 1; thus its sensitivity far exceeds any other physical instrument. The upper limit for perception of brightness is 10 lamberts—the brightness of white paper in full sunlight. The average brightness on a clear day out of doors, is 1 lambert, and at night 0.001 millilambert. At any given brightness, however, the eye adapts itself so that both the threshold and intensity of sensation are altered. Our powers of brightness discrimination are generally explained along the lines of Hecht's theory, viz., that in the sensory elements of the retina, which are adapted for a given intensity of light, photochemical processes are set up

whenever the eye is exposed to a light of a just discriminable higher intensity. When the eye is fully adapted to absolute darkness its sensitivity is greatest, and its threshold the lowest, but the perception time is increased and the stimulus must act for a longer time. Two factors must, therefore, be considered when dealing with the sensitivity of the retina: (1) the energy incident on the retina, and (2) the time during which it acts.

The energy itself is dependent upon two factors: (1) the intensity of the light, and (2) the area of the retina exposed. A general law has been formulated, the Bunsen-Roscoe Law, showing the relation between the intensity of light and the action of photochemical substances, such as the deposition of metallic silver on photographic plates from silver salts. To produce a given effect the product of the intensity of the light and the time during which it acts must be constant. This will be evident to those who use a camera. Out of doors a very short exposure is necessary, indoors a very much longer one. In many of the lower animals the Bunsen-Roscoe Law holds rigidly. Data on the human eye given in Table V show that for flashes of light of short duration the product of $I \times T$ is nearly a constant. As the duration of the flash increases, more and more energy is required to reach the threshold of stimulation, until eventually when the flash is of relatively long duration the threshold depends on intensity only, i.e., $I =$ a constant. The area of retina exposed also modifies the threshold. When sufficiently small areas are illuminated, the transition from the relationship $I \times T = C$ to $I = C$ is more abrupt than with larger areas. This means that for the eye as for other excitable tissues, such as nerve, there is a certain critical length of time through which the stimulus must act in order to produce an effect.[14]

TABLE V

TIME (SEC.) (T)	THRESHOLD IN MILLILAMBERTS (I)	I × T
0.002	0.00036230	0.0672
0.006	0.0009752	0.058
0.011	0.0004458	0.050
0.020	0.0002394	0.048
0.034	0.0001228	0.042
0.160	0.000706	0.0511
0.250	0.000512	0.013
0.500	0.000345	0.018
1.000	0.000262	0.026
2.000	0.00077	0.015
4.000	0.00063	0.025

In the dark-adapted eye the threshold is 0.0000007 millilambert. If now the eye be adapted to a brightness of 2,000 millilamberts, the threshold becomes 3.98 millilamberts. If a dark-adapted eye be suddenly exposed to light having an intensity of 25 millilamberts, its sensitivity drops to $\frac{1}{16}$ in five seconds, and a rest of ten minutes in the dark is insufficient to restore its original sensitivity. As a further example of change in sensitivity, it may be mentioned that a dark-adapted eye can stand a glare of only 25 millilamberts, while an eye adapted to bright sunlight can bear 16,000 millilamberts.[17]

The rate of this adaptation is of importance. If the change in brightness is small, the adaptation is almost instantaneous. In the change from brightness to complete darkness the eye adapts quite rapidly for the first few minutes, then

continues to adapt slowly for several hours, although for practical purposes it may be considered completely adapted in less than an hour.

According to Hecht[19] the curve showing the relation of the intensity of the light to the rate of adaptation is the isotherm of a bimolecular reaction, that is, it corresponds to the curve showing the quantities of two substances still uncombined at any given moment in a reaction involving the production of a third compound from two simpler ones at a constant temperature. The temperature in this case would, of course, be body temperature. The process can be illustrated thus:

$$S \xrightleftharpoons[\text{dark}]{\text{light}} P + A$$

S is a photosensitive substance, e. g., visual purple, which in the light breaks down (a monomolecular reaction) into the hypothetical substances *P* and *A*. In the dark *P* and *A* unite to form *S* (a bimolecular reaction).[19]

Investigations of Adrian and Matthews[2] on the electrical responses of the eye of the frog and eel to different intensities of illumination have led to similar conclusions as to the general course of the photochemical changes taking place in the retina.

One realizes the slowness of the change from light adaptation to dark adaptation when one comes into the house after having been out of doors on a bright sunny day when the ground is covered with snow. The reverse change from a low to a high intensity of light is more rapid. When colored lights are used, it is found that adaptation to red is more rapid than for any other color, but does not proceed to such a degree as for blue light; then come in order green, white, and finally yellow light. If care is taken to distinguish between adaptation in the fovea and in the periphery of the retina, it is found that in foveal dark adaptation the decrease in threshold is limited in extent, having a range of 100 to 1, and is rapid, being complete in three minutes; in the periphery the change is extensive, having a range of 10,000 to 1, and is slow, taking thirty minutes.[21]

These differences in foveal and peripheral vision have strengthened our belief in the duplicity theory. Since only cones are found in the fovea, they must be the sense organs for perception of color, and for clear, sharp vision, while the rods, located peripherally, must be the sense organs for colorless, dim vision.

The relation between the size of the test object and the sensitivity of the retina again brings out the fundamental difference between foveal and peripheral vision. If the area of the test light be increased gradually, it is found that its visibility varies directly with the visual angle up to a value equal to the angle of the fovea. In other words, visibility in foveal vision varies directly with the number of cones involved. But with further increase in the size of the test spot, the increase in visibility falls off as the more peripheral regions of the retina become stimulated; that is, the visibility does not keep pace with the number of rods stimulated.[36] This may be related to the fact that at the periphery of the retina many rods connect with one optic nerve fiber, while in the fovea it will be remembered that each cone has a nerve fiber to itself, but it is more probably accounted for in the fundamental differences in the action of the rods and cones as shown in the so-called "critical frequency" experiments.

Discs with portions cut out, or with various white and black or colored areas marked on them, are rotated at a certain distance from the eye. The rate at which the effect just ceases to produce a flicker and resolves into an unbroken sensation, is known as the "critical

frequency." The critical frequencies for white light of different intensities when plotted against the logarithm of the intensities give a straight line which breaks abruptly at about 0.25 candlemeters. At this same intensity there is an abrupt change from color vision to gray vision. If monochromatic light of short wave length, e. g., blue light, is used, the change occurring at the break in the illumination—critical frequency curve—is even more striking. The blue hue of the light vanishes and is replaced by a colorless or gray appearance, as we would expect, but for the lower intensities it is found that the critical frequency becomes a constant which is independent of the illumination.[23] In this respect the rods appear to act on the "all-or-nothing" principle, that is, the sensation is independent of the strength of the stimulus which aroused it.

Retinal Sensitivity.—One test of the sensitivity of a tissue is the value of its "chronaxie" (see page 12). The chronaxie of the human eye is found to have two values depending on the position of the stimulating electrodes. Near the periphery it is small, 0.001 to 0.0019 sec.; at the fovea it is larger, 0.0021 to 0.0028 sec.[51] This again shows that the rods are more sensitive than the cones.

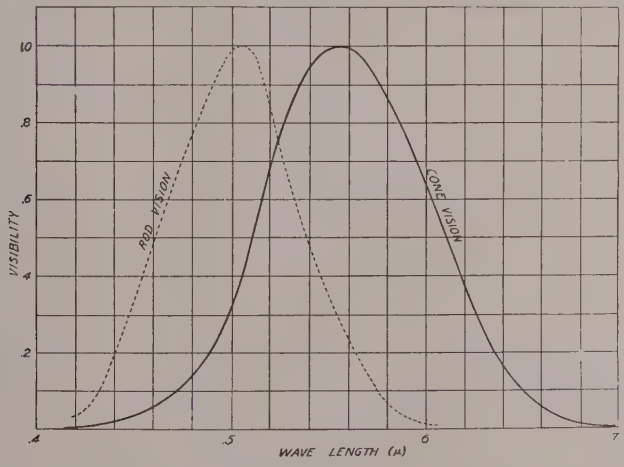


Fig. 90.—Visibility curves.

Furthermore, two different chronaxies have been found for the optic nerve, the larger being associated with excitation of the fovea, the smaller with excitation of the periphery of the retina.[4]

One of the difficulties encountered in an attempt to estimate the exact sensitivity of the retina is the fact that the amount of radiant energy necessary to produce a fixed sensation of brightness varies enormously with the wave length of the light. The absolute limits of visibility are 330 $\mu\mu$ in the ultraviolet for the dark-adapted eye and 900 $\mu\mu$ in the infra-red, if the latter is sufficiently intense. The usual range lies between 396 $\mu\mu$ and 712 $\mu\mu$. The yellow-green part of the spectrum appears to be the brightest for the normal eye, and therefore, less energy is required to produce a sensation by light of a wave length of from 500 to 555 $\mu\mu$ than by light of any other wave length. The actual amount of energy expended in just producing a sensation with light of a wave length of 550 $\mu\mu$ is 0.0015 Watt per lumen (1 lumen = the light emitted by a source of 0.07958 spherical candle power). Ten thousand times this amount is required in

the blue-green and red, and ten thousand times this amount in the extreme violet and extreme red.[23] The curve showing the relation of visibility to wave length is called the "visibility curve" (Fig. 90). The maximum of the visibility curve for the light-adapted eye is, of course, in the yellow-green.

If the spectrum is thrown on a screen and the screen is moved farther and farther away from the eye, the intensity of the spectrum decreases gradually, the colors become dim, and the maximum brightness shifts from yellow-green (550 $\mu\mu$) to blue-green (510 $\mu\mu$). If the screen is moved still farther away, the colors disappear altogether, leaving only a gray band with its brightest area where the blue-green had been. This shift, originally described by Purkinje, is known as the "Purkinje effect." This is shown in Fig. 90. It is evident at once that the cones are responsible for the brightness of the colors, and the rods for the brightness of the gray band. The same phenomenon is shown by varying the intensity of the incident light instead of the distance from the eye. If the eye is thoroughly light-adapted, however, the maximum brightness remains at 550 to 555 $\mu\mu$ for both foveal and peripheral vision, though under the usual experimental conditions no color is seen in peripheral vision. In the dark-adapted eye in dim light the maximum brightness shifts to 510 $\mu\mu$.

Fig. 91.—Color characteristics.

Color Sensitivity.—Practically all of the 80 odd theories of color vision are built on the assumption of the presence of a photosensitive substance, or substances, in the cones which can be affected by colored light in a manner similar to the bleaching of visual purple by white light. The sensation of light produced by radiant energy incident upon the retina may be said to consist of the two factors, color and brightness, the former being dependent on the wave length, the latter on the intensity of the incident light rays. The curve representing the relation between wave length and intensity gives the complete *physical* specifications of the quality of the incident light.[25] To describe the sensation completely a third quality must be added, namely, purity or saturation. These three attributes of color have been defined by the Committee on Colorimetry of the Optical Society of America, in their report for 1920-21.[48] (1) "Brilliance is that attribute of any color in respect to which it may be classed as equivalent to some member of a series of grays ranging between black and white." Synonymous terms are "brightness" or, in the artist's sense, "value."

Some 660 steps in brightness can be recognized by foveal cones. Too intense brightness gives rise to discomfort. This is known as "glare." Consideration of glare is of great importance in modern lighting systems. For example, at night the average brightness is 0.001 millilambert, and to an eye adapted to this dim light a sudden flash of light of an intensity of 186 millilamberts is distinctly uncomfortable.[38] Automobile lights are usually of greater brilliance than this. For work requiring continued application of the eyes it is found that the illumination of the surface to be looked at should reflect or transmit a luminosity of approximately one lumen per square foot. Less than this causes fatigue, more causes glare and asthenopia or discomfort. Optical and illuminating engineers should adjust the lighting so that there is a safe maximum of intrinsic brilliance for direct vision. This amounts to 1.75 to 5 candle power per square inch of apparent light source.

(2) "Hue is that attribute of certain colors in respect to which they differ characteristically from the gray of the same brilliance and which permits them to be classed as reddish, yellowish, greenish, or bluish." The hue is determined by the wave length.

Table of Color and Wave Lengths

0.723 μ to 0.647 μ = Red	0.575 μ to 0.492 μ = Green
0.647 μ to 0.585 μ = Orange	0.492 μ to 0.455 μ = Blue
0.585 μ to 0.575 μ = Yellow	0.455 μ to 0.424 μ = Indigo
0.424 μ to 0.397 μ = Violet.	

(3) "Saturation is that attribute of all colors possessing a hue, which determines their degree of difference from a gray of the same brilliance." Synonymous terms are purity and chroma. These three characteristics of color are best illustrated by the three dimensions of a solid, as indicated in Fig. 91.

PRIMARY COLORS

The question of color vision is inextricably bound up with the question of the physiology of the cones. We should know first of all what are the adequate stimuli for these sense organs. Although the eye is able to recognize about 180 different colors in the spectrum, there are a certain few primary colors, combinations of which can give rise to all the rest. The evidence now appears to be overwhelmingly in favor of the three colors, red, green, and violet, for the fundamental or primary colors. From these three not only all other colors, but also white, black, and gray, can be obtained.

The first piece of evidence is found in the three-color excitation or sensation curve shown in Fig. 92. These curves indicate in what proportions of intensity elementary hues must be mixed in order to match the hues of the various parts of the spectrum. Thus, to produce the same sensation as a spectral green of wave length 500 $\mu\mu$, a mixture of 123 parts of violet, 260 parts of green, and 83 parts of red is required. Naturally to obtain such curves it is necessary to adjust the values both of luminosity and color sensitivity to an equal energy spectrum. The values in Fig. 92 are all referred to average noon sunlight. From these curves can be derived the chromatic stimulation value of any given distribution of radiant energy.[25] This means that the sensation excited by any given wave length of the spectrum is really made up of red, green, or violet sensations in proportion to the ordinates at the given wave length.

A second piece of evidence is given by the "persistency curves."

Two different after-effects of light stimulation occur; these are termed positive and negative after-images. Light does not attain its maximum effect on the retina immediately

after it strikes it, nor does its effect cease immediately after the stimulus ceases to act. There is a waxing phase and a waning phase. After the stimulus has ceased to act, the sensation persists for a certain length of time growing fainter and fainter until it dies away. This after-effect is the positive after-image. The length of time the positive after-image persists is dependent on the strength of the luminous stimulus, according to Helmholtz. Thus, the positive after-image of the sun may last several minutes, while that of a moderately lighted object usually lasts not more than two seconds. This is true for colored as well as white light. To obtain the maximum effect the stimulus should last not more than 0.3 second. The cinematograph is a practical application of the physiological law of positive after-images. The succession of images is so timed that the after-image of each one carries the sensation on to the next, and a continuous and changing visual sensation results.

Negative after-images are caused by fatigue of the retinal elements. If one gazes steadily at a red character on a green background for half a minute, then quickly transfers his gaze to a uniformly lighted white or gray surface, he will see the character in green on a red background. The duration of the negative after-image is also proportional to the strength of the stimulus.

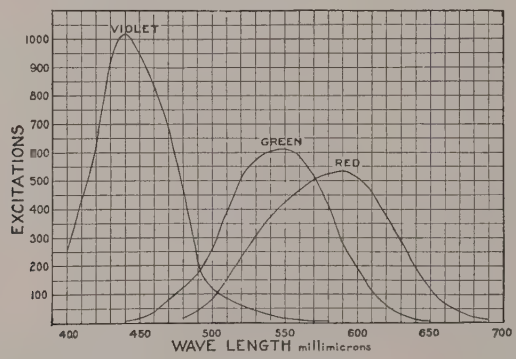


Fig. 92.—Excitation or sensation curve of the human eye for hue.

The after-image is, therefore, both positive and negative in character. If the observer closes his eyes after looking at a bright object or looks at a black surface, the after-image is positive, but if he looks at an illuminated surface the after-image is negative. The after-image of a very bright object changes in absolute darkness from positive to negative, then back and forth until after four or five minutes only a sensation of faint gray light remains. This is claimed to be due to automatic variations in retinal activity, independent of the action of light.

If the eye is stimulated and fatigued by looking for three minutes at a given color, and the time the color sensation persists after the stimulus has ceased to act is plotted against the wave length, the resulting curve is known as the "persistency curve." If this is done in diffuse daylight, in a dimly lighted dark room, or the eye kept in the dark or blindfolded when the stimulus is shut off, the four curves have the same general form, but they are by no means identical. In the dark the persistence is greater than in daylight, but not equally so for different wave lengths. For orange light the persistence time is 3 per cent greater in the dark than in daylight; for red, 12 per cent; for violet, 30 per cent. Allen found that the persistence time is inversely proportional to the logarithm of the luminosity. From this relationship he was able to plot luminosity curves for the different wave lengths. These luminosity curves prove to be composed of two straight lines of different slope, the change in direction occurring abruptly.

One line evidently represents the response of the cones, the other, the rods.[8] According to this investigator the spectrum is to be viewed as in the diagram in Fig. 92. All other colors of the spectrum are to be regarded as composite except red, green, and violet. The fundamental red sensation corresponds to some hue between the beginning of the red and the point of transition at 0.630 μ. Similarly the fundamental green sensation is excited by some portion of the spectrum lying between the second and third transitional points at the wave lengths 0.570 μ and 0.470 μ. Finally the third fundamental sensation, which must be violet and not blue, as many color-theorists allege, lies between the fourth point of transition at 0.420 and the end of the violet.[8]

YOUNG-HELMHOLTZ THEORY OF COLOR VISION

The fact that the number of primary colors can be limited to three was recognized by Young more than a century ago, and was used by him in formulating his theory of color vision. As modified by Helmholtz this theory states that there are three types of cones, each type having its own peculiar photosensitive substance, one responsive to red light, another to green, and the third to violet; stimulation of certain combinations of the three types gives rise to all the different color sensations; stimulation of all three equally gives white; absence of stimulation gives black.

A person, born blind, whose sight was gained at the age of twenty-two appreciated white first, then red, then green, and finally the other colors.

We readily recognize that many colors do appear to be mixtures, e.g., we call hues between blue and green "greenish blue" if they are nearer the blue end of the spectrum, and "bluish green" if they are nearer the green. Yellow, however, by no means appears to be a mixture of red and green, although in the spectrum it lies between these two primaries. We speak of reddish yellow and greenish yellow as if yellow were a primary. White also does not suggest a mixture. To account for such phenomena other theories of color vision have been formulated with the emphasis on the nature of the sensation aroused, in opposition to Young's, which emphasizes the nature of the stimulus. The former type of theory, however, fails to take into consideration the fact that if a suitable red field is presented to one eye and a suitable green field to the other, the resulting sensation is yellow. There is no need, therefore, to suppose that a special receptor is required for yellow.

It is to be noted that the Young-Helmholtz theory tacitly assumes the validity of the doctrine of "specific nerve energies" (Johannes Müller), i.e., that the nature of the nerve impulse is the same no matter what nerve is stimulated, an assumption which has been strongly fortified by recent experimentation.

COLOR BLINDNESS

Color blindness was first accurately described by the English chemist, John Dalton, in 1774. He was unable to see any difference in color between "a laurel leaf and stick of red sealing wax," and the colors of the rainbow narrowed down to yellow and blue. The phenomenon is not so rare as first supposed. Nine per cent of otherwise normal and healthy men and 2 per cent of women are color blind to a certain degree. According to the Young-Helmholtz theory color blindness would be due to abnormality in one or more of the three types of cones, and we might find 7 types of color blindness.

(1) Red-blind
(2) Green-blind
(3) Violet-blind
(4) Red-green-blind
(5) Red-violet-blind
(6) Green-violet-blind
(7) Red-green-violet-blind.

In examination of 27 color-blind persons Allen found all of these types except the violet-blind. There were 5 red-blind, 4 green-blind, 9 red-green-blind, 7 red-violet-blind, 1 green-violet-blind, and 1 red-green-violet-blind. The visability curve has been plotted for several of these color-blind individuals. The shape of the curve is the same as for normal sight (Fig. 90), but its position may coincide with that for cone vision, i.e., with the maximum in the yellow-green at a wave length of 550 $\mu\mu$, or with that for rod vision with the maximum at 510 $\mu\mu$, or anywhere between the two.[3]

If a large group of persons having apparently normal color vision is tested with care for their ability to match colors, certain of them will be found to require different proportions of red and green to match a given yellow from the others. Such persons are called "anomalous trichromats." It is assumed that in anomalous trichromats all three cone types function, but in a slightly different manner from truly normal persons. Red-green-blind individuals (4 per

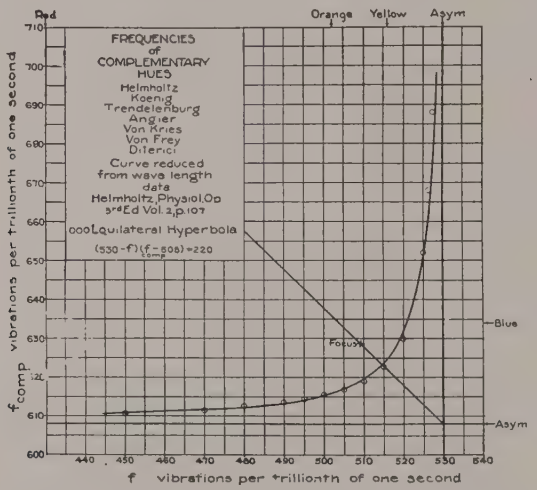


Fig. 93.—Relationship of frequencies of complementary colors.

cent of all men) are called "dichromats" on the assumption that one of the three photosensitive substances is lacking or so changed that it becomes identical with one of the other two. This class has been divided into "protanopes," the red-blind, and "deuteranopes," the green-blind. "Tritanopes," the violet-blind, are rare.

The terms "protanope" and "deuteranope" have been made to include persons whose color system lacks both red and green; "protanopes" having the spectrum shortened at the red end, "deuteranopes" being able to see color throughout the whole spectrum. It must be noted that even persons with normal color vision are found to vary from day to day with regard to the exact range of the colors they see in the spectrum, such as the yellow, and in their ability to locate the central portion of that color.

Since presentation of red to one eye and green to the other gives rise to a sensation of yellow, the theory has been proposed that color perception is essentially the result of central rather than peripheral activity. An argument advanced in favor of this idea is that through hypnosis persons with perfectly normal color sense can become red, green, or red-green color blind.

Total color blindness is always associated with nystagmus (pp. 145, 280) and central scotoma. The spectrum appears as a gray band, the maximum brightness is the same as for scotopic vision, and it is probable that the cause is defective development or complete absence of cones.

COMPLEMENTARY COLORS

All the colors of the spectrum can be grouped into pairs in such a way that a mixture of the two in the proper ratio of intensities yields white. Such colors are said to be complementary to each other. Red and blue-green, yellow and blue-violet, are examples of complementary colors. For green there is no complementary color in the spectrum, its complement is purple, halfway between red and blue. For this reason the line representing hue in the color solid (Fig. 91) is a complete circle, the center of which represents gray. The wave lengths can be so spaced about the circumference of this circle that complementary colors lie at the ends of diameters, indicating that mixture of complementary colors gives gray. The relation between complementary colors is shown in a curve obtained by plotting their wave lengths against each other. The curve is a hyperbola, but two-thirds of the data fall on one side of the vertex of the curve. If their frequencies* are plotted instead of their wave lengths, the curve is a perfect rectangular hyperbola (Fig. 93), the asymptotes of which are found to correspond with the neutral or colorless points in the vision of the color-blind person. On one side, the asymptote 530 corresponds with 522, the neutral point for the "yellow-blue-blind"; and on the other, 608 corresponds with 612-601, that for the "red-green-blind."

*Frequency per trillionth of one second $= \frac{300{,}000}{\text{wave lengths in millimicrons}}$.

CHAPTER XXIV

EYE MOVEMENTS

The Lids.—Movements of the eyelids are brought about mainly by the action of two muscles, for opening the eye, the *levator palpebrae superioris*, and for closing it, the *orbicularis palpebrarum*. The former muscle is innervated by a branch of the third nerve, and the latter by the seventh.

Acting in conjunction with the *levator* there are also smooth muscle fibers, innervated by the sympathetic. The difficulty in maintaining one's eyes open during fatigue is due to a lowered state of tonus in these smooth muscles; the lids must then be voluntarily raised by the levator and the frontalis muscle as well.

The wink or the corneal reflex is of importance in administering anesthetics, for it is practically the last reflex to disappear in anesthesia. The stimulus for the wink reflex may be contact of the eye with a foreign body, the motion of an object toward the eye, irritation in the nasal mucosa leading to sneezing, etc. It is generally considered that the central part of the cornea is sensitive to pain only and not to touch; and since histological examination of the cornea shows that the only possible sense organs present are free nerve terminations of the ophthalmic branch of the fifth nerve, this has been considered evidence that the sense organs for pain are free nerve terminations. The periphery of the cornea is sensitive to cold, and the distribution of cold spots is found to correspond with the distribution of Krause's end bulbs.

Because the wink reflex is so easily elicited and registered it has long been a subject for experimentation. Its chronaxie in both man and the cat is about 0.6 msec. It can be used in the establishment of conditioned reflexes to light, sounds, and other stimuli. If, however, the cutaneous area, stimulation of which ordinarily causes a wink, is rendered insensitive by application of a local anesthetic, conditioning stimuli are ineffective; this means that the reflexogenous area of the unconditioned reflex arc must remain intact in order for the conditioned reflex to be carried out.

Small mirrors have been attached to the lids and records taken of the movement of light reflected from them in winking. It is found that the upper lid moves inward as well as toward the lower lid. At the same time there is a very rapid movement of the eyeball upward and inward. The amount of movement is of the order of 10 to 15 degrees on the arc of vision. This opposing telescoping action of lid and eyeball obviously results in a more prompt protective covering of the cornea. If one notices carefully, one can observe while reading, that just at the beginning of the wink reflex it appears as if the page were suddenly jerked downward. This reflex may explain the rolled-up position of the eyeballs during sleep. When the lid is lifted, the movement of the eyeball is in the reverse direction, though made slower.[34]

Part of the orbicularis muscle, the pars lacrimalis or Horner's muscle, has a very important function in the disposal of the products of secretion of the lacrimal glands. The fluid under ordinary circumstances is secreted only in a quantity sufficient to replace that lost by evaporation. The liquid flows from beneath the lateral part of the upper eyelid down across the eye to the lower lid, where it is prevented from running over the edge by the greasy lubrication

of the tarsal glands. In the process of winking the cornea and front of the eye are lubricated. Excess of the fluid enters through the puncta, and reaches the lacrimal sac through small canals, thence it passes to the nasal cavity. The lacrimal sac in the normal condition is flattened from side to side so that its lumen is a mere cleft. During the act of winking contraction of Horner's muscle dilates the sac which aspirates the liquid lying along the edge of the lid, and causes it to enter the sac. This can be demonstrated in cases of paralysis of the orbicularis when tears can be made to enter the sac by drawing the lids laterally. When the lid is lifted, the lacrimal sac regains its normal and reduced capacity, owing to the elasticity of its walls, and the contents will be driven on toward the wider channel of the nasolacrimal ducts rather than backward through the narrow canaliculi. The capacity of the lacrimal sac during ordinary winking is increased by 2 c.mm., and during forced effort by as much as 30 c.mm. An enzyme has been found in tears capable of destroying bacteria.

The Extrinsic Muscles.—The six extrinsic muscles of the eyeball, the four recti and two obliques, are responsible for its movements. These take place about an axis which lies 13.5 mm. back of the cornea, or very near the geometrical center of the eyeball. The four recti muscles are attached somewhat on a slant so that although the internal and external recti cause lateral movement in a horizontal plane, neither the superior nor inferior recti can produce movement in a purely vertical direction. The superior rectus causes movement of the eyeball inward as well as upward, and there is also some rotation of the cornea (torsion) so that the vertical meridian assumes a direction from above down and out. Similarly the inferior rectus causes movements inward as well as downward. To counteract this torsion effect the inferior oblique acts in conjunction with the superior rectus, since it pulls the eye upward and outward, and the superior oblique with the inferior rectus, since it pulls the eye downward and outward. The obliques are especially called into play when the eyes are convergent. For coordinated movement it is, of course, essential that an opposing muscle relax as its antagonist contracts. Sherrington found the eye muscles particularly useful for demonstrating the principle of reciprocal innervation of antagonistic muscles (see page 112). Two methods are now in vogue for registering eye movements; the more common one involves photographing reflections from the corneas of the two eyes; the other involves recording action potentials through electrodes attached to the skin adjacent to the eyeballs. It is claimed that the latter method has the advantage that the head does not have to be fixed and the procedure can be carried out in the dark. The former method has been widely used in determining eye movements during reading. It is found that the eyes do not move at a steady pace but fixate and then move rapidly to a new position of fixation. Strangely enough, the eyes appear to make slight divergent movements during the fixation periods, and convergent ones between fixations, so that the two eyes do not make strictly parallel movements as originally thought. These coordinated eye movements in reading are interfered with if the oxygen supply to the brain is cut down. When a degree of anoxemia equivalent to an elevation of 18,000 feet is maintained, there is an increase in the number of fixations, decrease in divergence, and the appearance of nystagmus.

In close relation to Tenon's capsule is found a scattered and ill-defined area of smooth muscle fibers, innervated by the sympathetic system. It has been

considered by some that contraction of these fibers due to pressure of the enlarged thyroid in the cervical region, was the cause of the exophthalmos of goiter. The prevailing opinion, however, is that this condition is caused by dilation of the orbital blood vessels through excitation of the sympathetic nervous system.

Exophthalmus can be produced experimentally in the guinea pig by injection of anterior pituitary extract after thyroidectomy. This state can be considerably reduced by administration of thyroxin, but not by administration of sodium iodide.

Reflex Response to Changes in Position of the Head and Body.—The relation of the position of the body to the position of the eyes is nicely adjusted by reflexes originating in the labyrinth and neck. Magnus has shown that the eyes tend to take up a position such that their visual fields suffer as little change as possible when the position of the head and neck is changed. For labyrinthine stimuli the external and internal recti take no part in the response; only those eye muscles used in compensating for movement or rotation in some other than the horizontal plane are affected. When, however, the head is moved with relation to the body, and the proprioceptive sense organs in the neck are affected, then all the eye muscles are brought into play. These are the so-called static reflexes, the response to abnormal orientation; but the eyes also respond to *movement* of the head, such as angular accelerations, movements of rotation, or progressive acceleration along a straight line.

If a person is rotated, say to the right, the eyes turn in the opposite direction in order to preserve fixation. The eyes soon reach their limit of movement to the left and quickly turn back to their primary position. This movement is known as *nystagmus*. There are, therefore, two components to nystagmus, the first being a slow movement, the second a quick one. The direction of the nystagmus is the direction of the quick return movement. At the beginning of rotation nystagmus will therefore be in the direction of the rotation. If the rotation is continued at a fairly rapid rate, there is no movement of the eyes, but upon stopping rotation there is again nystagmus, the quick component of which is in a direction opposite to the rotation.

The older theories, in which the stimulus to eye movement was considered to be motion of endolymph in the semicircular canals affecting the cristae of the semicircular canals, are no longer held. According to Maxwell[32] the cristae of the semicircular canals are stimulated by changes in tension in the utricular membrane caused by inertia effects in the larger bodies of fluid in the utricle and vestibule. Ivy[24] claims that the movements of the eye in nystagmus are not due solely to stimulation of the labyrinth, but that proprioceptive reflexes from the eye muscles themselves must play a distinct part in the movements. The cerebral cortex is not necessary for nystagmus since nystagmus is present after removal of the cerebrum, including the occipital lobes. Injury to the superior colliculus impairs movements of the eye on the side opposite to the injury.

Postrotatory nystagmus may last twenty seconds in response to a stimulus lasting a fraction of a second, and it is difficult to explain this fact if the inertia of the endolymph in the semicircular canals alone is involved.

BINOCULAR VISION

When a person with normal vision focuses his gaze upon an object either far or near, although two images are formed, one on each retina, and the nerve impulses aroused affect areas in different halves of the cerebral cortex, yet he sees the object singly. Seeing double, or the condition of diplopia may be monocular, but it is more generally a consequence of faulty binocular vision, and this means improper balance in the eye muscles. For example, if the internal rectus of one eye is congenitally small or weak, that eye may turn outward,

owing to the unbalanced action of the external rectus. Tendency for the eye to turn outward is known as exophoria, and if the eye is actually turned out the condition is known as *divergent strabismus*. The tendency to turn the eye in is known as esophoria, the condition as *convergent strabismus*. If the eye tends to rotate or intort, this is known as cyclophoria. These defects can be detected by having the subject fixate upon some point. The observer now covers one eye of the subject and notices any change in position of the other eye while the subject continues to fixate upon the same point. If the eye shifts its position, strabismus is present. This is known as the *cover test*.

For both far and near vision the image of the object upon which the gaze is fixed should fall on the fovea. This means that for very near vision the eyes must converge strongly. It can readily be shown that we do see double images of objects not quite in focus.

If one index finger is held about ten inches from the face, and the other as far from the first as possible, but in a horizontal line with it, upon fixing the gaze on the far finger the near finger is seen double. If now the right eye is closed the left one of the double image disappears. If the gaze is directed toward the near finger, the far finger is seen double. But now upon closing the right eye it is the right one of the double image which disappears. The explanation will be evident from a study of Fig. 94.

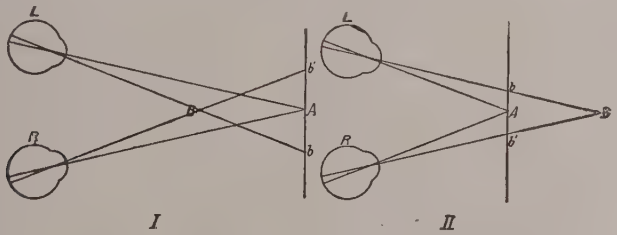


Fig. 94.—*I*. The gaze is fixed on far point *A*. A double image of *B* is seen at *b* by the left eye, at *b'* by the right eye. If the right eye is closed, *b'* disappears. *II*. The gaze is fixed upon the near point *A*. A double in eye of *B* is seen at *b* by the left eye, and at *b'* by the right eye. If the right is closed, *b'* disappears.

In order that an object may be seen singly the points of the image of that object must fall on *corresponding points* of the two retinas; if they fall on disparate points the object will be seen double (binocular diplopia). It is evident that points in the fovea of the two eyes are corresponding points, and that points on the nasal side of one retina and on the temporal side of the other are corresponding points. The position of corresponding points in the two retinas will change with the fixation distance. At each fixation distance there is an imaginary curved surface, such that each point in it forms an image which falls on corresponding points in each retina. Objects nearer or farther away than this surface will be seen double. This curved surface is called the *horopter*. Normally we tend to ignore images falling on disparate points and are conscious only of the objects seen singly. If something about the object seen double attracts the attention, the eyes are at once moved so that it is seen singly.

It appears to be a physiological law that an object is perceived in the direction of the unrefracted ray impinging upon the retina. A person with diplopia attempting to fixate on an object can get only one eye in an axial line with the object; with the other eye the object is seen to one side of the axial line, and furthermore the image seen with this eye is nonmacular. There is, therefore, a mental conflict, and usually the image formed on one retina

is disregarded. This is not so uncommonly the case even in persons with normal binocular vision. One eye very often does the majority of the work. An extreme case is seen in persons who are accustomed to keep both eyes open while using a monocular microscope, and in some cases the individual is able to look at the object under the microscope with his left eye and see his pencil and paper clearly enough with the right to trace the image of the object on the paper.

To see clearly any object nearer than the far point, two processes are brought into play: accommodation and convergence. For practical purposes the far point is fixed at 6 meters for the normal eye at rest, and with its axes parallel. In reality the far point for accommodation varies with the size of the pupil, and the far point for convergence with the interpupillary distance. Expressed in meters for accommodation it is equal to 7.5 times the distance between the pupils in millimeters.[27] Both accommodation and convergence increase at the same rate as an object is brought nearer the eyes, i.e., both vary inversely as the distance which separates the object and the eyes. If the object is 1 meter away, then there is $\frac{1}{1} = 1$ unit of accommodation = 1 diopter; and $\frac{1}{1} = 1$ unit of convergence = 1 meter angle. A simple experiment shows that both accommodation and convergence occur in both eyes at the same time.

The observer screens the eye of an emmetropic subject so that the subject is unable to see a certain object with this eye, but the observer is so placed that he can see the movements of both eyes of the subject. The screened eye will be found to make the same effort of convergence and accommodation as the free eye. If the screen is suddenly removed no further eye movements are made, nor does the object appear double or blurred to the subject. If now the subject accommodates for far vision and in front of the free eye is placed a concave lens, a surplus amount of accommodation is required as if the object were brought nearer, and the free eye becomes artificially hypermetropic. The screened eye under these circumstances immediately turns inward, i.e., the eyes converge instead of keeping parallel. Convergence and accommodation thus proceed equally in the normal eye. We might expect to find a convergent strabismus in persons naturally hypermetropic, and this is very often the case. But because the hypermetrope fixes one eye, and ignores the image formed in the other, it appears to an observer as if one eye alone is deviated.

CHAPTER XXV

THE EAR AND HEARING

In the ear there are two kinds of sense organs, one, an exteroceptive organ for which the stimulus is a vibrating body, the second, proprioceptive organs, for which changes in the position of the head are the stimuli. The hearing sense organ lies in the cochlea and is innervated by the cochlear branch of the eighth nerve. The organs of position include the semicircular canals, the utriculus and sacculus; these are innervated by the vestibular branch of the eighth nerve.

TRANSFERENCE OF ENERGY FROM SOUNDING BODY TO RECEPTOR CELLS

In order that a vibrating body may produce an audible sound, there must be communication of the vibration over a suitable material medium. Usually the air is this medium. There is no sound from a body vibrating in a vacuum. Furthermore, the vibrations must be of a certain intensity in order to produce a sound. While a tuning fork is vibrating in the air, alternate condensations and rarefactions of the air radiate out from the fork.

These "sound waves" reach the external auditory meatus and are reflected from the bottom of this bony tube so as to strike perpendicularly on the tympanic membrane, which closes the inner end of the tube, and sets it into motion (Fig. 95). The handle of the malleus, the first of the chain of three small bones in the middle ear, is attached to the tympanic membrane and consequently both the membrane and bone vibrate together. The malleus is connected with the other two bones, the incus and stapes, so that they vibrate also. The end of the stapes acts as a plunger into the oval window, a hole in the temporal bone opening into the scala vestibuli of the membranous labyrinth (Fig. 96). A push inward on this plunger displaces the perilymph, the liquid in the scala vestibuli of the cochlea. Running beneath this chamber in the cochlea is another chamber, the scala tympani, also filled with perilymph. These two chambers are connected with each other only through a small opening, the helicotrema, situated at the apex of the cochlea, so that pressure in one chamber is communicated to the other with difficulty through the small opening. But lying between these two chambers is a third, the scala media, filled with endolymph, and opening into the sacculus. Between the scala vestibuli and the scala media is a thin membrane, the membrana vestibuli; and between the scala media and the scala tympani another membrane, the basilar membrane. A bony partition separates the scala vestibuli from the scala tympani, so that pressure on the perilymph in the scala vestibuli is communicated through the endolymph in the scala media to the perilymph in the scala tympani. The pressure is relieved by the bulging into the air-filled middle ear of the membrane which covers the end of the scala tympani at the round window, the fenestra rotunda. This whole chain of events takes place with each movement of the tympanic membrane, so that when it is thrust inward the membrane at the round window bulges out, and when the tympanic membrane is drawn out, the membrane at the round window is drawn in.*

The part played by the *pinna* or auricle in man in the act of hearing is negligible, but in those animals whose ability to move their ears is retained, directing the pinna toward the source of the sound must be of distinct advantage.

That the *tympanic membrane* vibrates at the same rate that the sounding body vibrates, is shown in a number of experiments. The membrane may be gilded, or a small mirror attached to it, and when a tuning fork is sounded near

*Crowe and his collaborators have claimed that immobilization of the membrane at the round window increases by 50 per cent the ability to perceive sound.[22] Because of the importance of this finding for the amelioration of deafness, other investigators have attempted to confirm this result but so far without success.[7]

the ear, light reflected from the membrane will show excursions at the same rate that the tuning fork is vibrating. If the ear is connected up in such a way as to be a part of a gas chamber for a manometric flame, the flame shows excursions which could only result through vibration of the membrane, and the number again corresponds to the vibration rate of the sounding body.

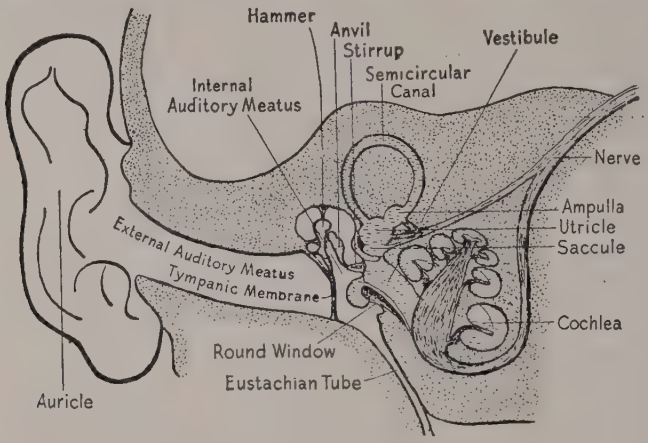


Fig. 95.—Relation of parts of human ear.

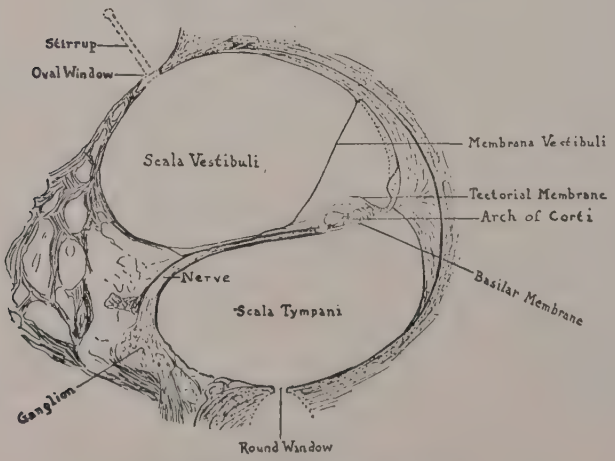


Fig. 96.—Section through cochlea.

That the *auditory ossicles* vibrate in a similar manner is shown by attaching delicate levers to them and recording their movements, or by sprinkling them with starch grains or some other substance, and following the movement of the particles under a microscope.

The correspondence in rate between vibrations of the sounding body, the tympanic membrane, and the auditory ossicles, is very exact. The tympanic

membrane, therefore, cannot act like a drum head which has its own vibration rate, but it must be aperiodic. Although the membrane is only 0.1 mm. thick, it is composed of three layers, the middle one being mainly responsible for the property of aperiodicity. This layer is composed of both circular and radial fibers whose tension is different at different points, owing to the fact that the handle of the malleus draws the membrane inward so that it has the shape of a hollow cone, and the apex of this cone is below its true center. These factors contribute not only to render the tympanic membrane aperiodic, but to prevent its continuing to vibrate beyond the time when the sounding body has ceased to vibrate. The radial and circular fibers in persons under fifty years of age contain collagen and stain histologically like true elastic tissue; in persons over fifty there is deposition of sclerosing fibers and the elastic fibers no longer stain well. It was earlier considered that simple incisions in the tympanic membrane caused no impairment in transmission of sound. This appeared to be borne out in records of the electrical responses of the cat's ear after such incisions. More recently, however, with improved methods of registration, it has been shown that in the cat small but consistent impairments result from such lesions, the nature and extent of the impairment depending on the site and extent of the lesion. The loss is relatively greater for tones of low frequency and high intensity, viz., 256 to 4,096 cycles per sec., and agrees with recent audiometric studies of the effects of simple traumatic rupture of the tympanic membrane in man.

The three auditory ossicles are fitted into each other in such a manner that they move like a lever. The fixed point or fulcrum of the lever is situated in the incus, and when the handle of the malleus is moved inward, the head of the malleus and the greater part of the incus move outward, while the long process of the incus and the stapes, which is attached to its end, moves inward. The lever arm on the malleus side is 1.5 times that on the stapes side, hence the excursion of the stapes is less than that of the handle of the malleus, but the thrust on the perilymph at the oval window is magnified. Furthermore, the area of the tympanic membrane is some 20 times that of the oval window, so that the force of the thrust at the oval window is actually about 10 times that at the tympanic membrane, when allowance is made for friction. A further advantage in the position of the fixed point in the incus is that practically equal masses of bone lie above and below it so that the ossicles are approximately in balance, and respond to very small movements. They rotate in one plane only.

Any interference with the free motion of the ossicular chain has a profound influence on the conduction of air-borne sounds, the impairment being somewhat greater for high than low tones. If, however, the sounding body is in contact with the head so that the vibrations are bone conducted, interruption of the ossicular chain has little effect, at least on the electrical responses of the ear.

Two *small muscles* are present in the middle ear: the *tensor tympani* which is attached to the handle of the malleus and is innervated by a small branch of the fifth nerve, and the *stapedius* which is attached to the neck of the stapes and is innervated by a small branch of the seventh nerve. The functions of these small muscles are somewhat problematical. It has been demonstrated that the contraction of the *tensor tympani* draws the handle of the malleus inward, and thus increases the tension of the tympanic membrane. It is found to be slack when no sounds fall on the ear, but contracts to auditory stimuli, and to stimulation of the pinna, external meatus, and the facial nerve. In certain mammals,

such as guinea pigs, subjection to a continuous tone of a given pitch first produces fatigue, then destructive lesions in the cochlea. If the tensor tympani has been removed, the destructive lesions appear earlier than if it is intact.[50] It has also been found that if this muscle is fixated so that it cannot contract, or if the tympanic membrane bulges inward through unequal pressure in the external ear and middle ear,[47] there is loss of conduction of low tones.[22] When the *stapedius* contracts, it pulls on the stapes laterally. The contraction of this muscle has been observed in a man with a perforated tympanic membrane when notes of various pitches were sounded and even in expectation of a noise.

During spontaneous contractions of these two small muscles in the ear of the guinea pig, it is found that the stapedius responds some 50 msec. earlier than the tensor tympani, but that the contraction of the tensor tympani overpowers and outlasts that of the stapedius. When they are both contracted there is impairment in conduction of tones below 1,000 cycles per sec., enhancement in tones between 1,300 and 1,800, and no effect on tones above 2,000. This indicates that the function of these two muscles is to protect the transmitting apparatus from too great an intensity of low tones, and to "tune it up" for reception of tones of about 1,500 cycles per sec.

The middle ear is filled with air, and opens through the Eustachian canal into the pharynx. In order for the tympanic membrane to function properly there must be equal pressure on each side of it. Upon ascending a tall building in an elevator, or descending the shaft of a mine, the difference in pressure on the two sides of the tympanic membrane may result in temporary deafness. Swallowing or yawning opens the entrance to the Eustachian canal, which under normal circumstances is closed, and the pressure is then equalized. A cold in the head often causes blocking of the Eustachian canal, in which case the air in the middle ear becomes absorbed, and the tympanic membrane is drawn tautly inward, and deafness results. When the canal remains blocked, piercing the membrane relieves the situation.

Occlusion of the pharyngeal orifice leads to greater impairment in the hearing of high than of low tones. It has been shown by manometric measurements that the Eustachian tube offers a resistance by 20 mm. Hg when the subject is in the erect position; the resistance is increased in the prone position and upon flexing the head toward the chest; it is decreased on swallowing and during exercise. If the tube remains open, direct transmission of the sounds of the person's own breathing and voice masks all extraneous sounds near their threshold.

Since unequal pressure on the two sides of the ear drums has so pronounced an effect on the transmission of sound, the effect of reduced atmospheric pressure as experienced in aviation has been the subject of special study. Atmospheric pressure must be reduced by 3-5 mm. Hg before the subject experiences any change. At this point he describes a sensation of "fullness" in the ear, and it is found that the tympanic membrane is decidedly bulged outwards. A further decrease of 15 mm. Hg gives rise to an uncomfortable "click" when the membrane snaps back to a more normal position and the "fullness" disappears. This is the result of the pharyngeal tube being forced open and the pressure equalized on each side of the membrane. The phenomenon is repeated as the atmospheric pressure diminishes until at relatively high altitude the air is so thin that it no longer forces the tube open. The pharyngeal tubes therefore act in the capacity of flutter-valves; on increased pressure they close and tend to stay closed.

The actual sense cells for hearing are hair cells located in the complicated organ of Corti on the floor of the scala media in the cochlea, the tips of whose hairs appear to be embedded in the tectorial membrane above. The reason for considering the hair cells to be the sense cells is merely that the endings of the

auditory branch of the eighth nerve terminate about them and about no other structures in the organ of Corti. Just how these are stimulated by changes in pressure in the liquids of the inner ear is still a matter of conjecture. Probably movement of the basilar membrane puts a strain on the hairs, upward movement bending them, downward movement pulling them. The stimulus thus set up is transmitted to the nerve fibers. This presupposes that the basement membrane is the structure in the organ of Corti which vibrates in harmony with the sounding body outside the ear.

Similar hair cells are to be found in the vestibular part of the inner ear, viz., in the cristae of the ampullae of the semicircular canals and in the maculae of the utriculus and sacculus. Branches of the vestibular branch of the eighth nerve terminate about these hair cells. Lying on the hair cells in the utriculus and sacculus, but not on those in the semicircular canals, are small calcareous concretions, the otoliths. The hair cells in the ampullae of the semicircular canals are supposed to be bent through the inertia of the endolymph when the head is moved, or upon cessation of prolonged movement. They are therefore said to be responsible for the kinetic sense. Because of the position of the three canals, two in the vertical plane at right angles to each other, the third in the horizontal plane at right angles to the other two (see page 144), movement in any direction in space should be detected. The functions of the utriculus and sacculus, however, are not so well established. It appears unsafe to deduce their function in man from the results of their extirpation and stimulation in such forms as the dogfish, which because of its cartilaginous skull has been a favorite animal for experiments on the vestibular apparatus. Because of their position, the macula of the utriculus being in the horizontal plane, that of the utriculus in a nearly vertical plane, and the presence of the otoliths, these organs are thought to be concerned with position, i.e., with static changes rather than with dynamic movements. Changes in position of the head probably cause a slight shift in the position of the otoliths with relation to the hair cells to which they are attached. In the frog by dissection, and in the guinea pig by centrifuging, the otoliths may be detached. Under these conditions the animal retains the reflexes concerned with rotatory movements, i.e., statokinetic reflexes, which must therefore be initiated by the semicircular canals, but is said by some investigators to lose its statotonic responses, i.e., the tonus of the muscles on the injured side is diminished so that the head is turned and the body curved. Other investigators, however, find that a frog with otoliths gone still retains its static reflexes but does not react to progressive movements. In general, however, the distinction still holds that the semicircular canals are more concerned with movement, the utriculus and sacculus with position.

CHARACTERISTICS OF SOUND

Subjectively a tone is said to have three qualities: loudness, pitch, and timbre. Two more are added by some psychologists: volume and duration. Loudness varies with the amplitude of vibration, pitch with the frequency of vibration, and timbre or quality with the pattern of the wave. The quality described as "volume" has reference to the impression of massiveness associated with low tones, and of smallness associated with high tones.

The range of vibrations capable of stimulating the human ear is from 16 to 20,000 complete vibrations per second. Below 16 we hear individual puffs of air from a wind instrument, or individual beats from a string. Although human beings do not perceive sounds above a rate of 20,000, cats can, and the upper limit varies in different individuals. In the middle range, i.e., between 100 and 1,000, the ear can distinguish differences in pitch of one vibration per second—some claim to be able to detect even a quarter of a vibration difference. At 3,000 the difference increment must be increased to 10 vibrations, and at 4,000 and above to 40 vibrations, to perceive a difference between the two tones. This means that

there are altogether about 11,000 different pitches the ear can detect. Therefore, there should be at least 11,000 hair cells, and the same number of fibers in the cochlear branch of the auditory nerve. McKendrick calculated the numbers of these structures and found them adequate for the Helmholtz theory.

Any theory attempting to account for the power of the ear to analyze sound has chiefly to explain how differences in intensity and differences in pitch are perceived, since the other characteristics of sound appear to depend on these two.

1. It is usually considered that the middle ear, including the tympanic membrane and auditory ossicles, is responsible for analyzing differences in intensity. According to this view the threshold of audibility would be determined by the least change in pressure which could set the system into vibration. It has been found that the threshold is not the same for all pitches. In passing from a certain middle range to either a higher or a lower pitch the threshold is raised. The lowest threshold of audibility lies in the neighborhood of C^4 which has a vibration frequency of 2048 per sec., and the energy required to produce a sensation is less than one-thousandth of a dyne. The upper limit at this pitch, beyond which the ear cannot tolerate the stimulus and discomfort ensues, is approximately one million times the threshold. Thus, the ear approaches the eye in sensitivity.

The unit of intensity of sound is the "bel." When the intensity is increased tenfold, it is said to be increased by 1 bel; one hundred fold, 2 bels, etc.

2. The inner ear, especially the structures in the organ of Corti, is held responsible for analysis of differences in pitch. No one of the present theories of pitch perception is acceptable both to the physiologist and to the physicist. In general, the theories come under two heads: (a) those which assume that the parts of the organ of Corti vibrate as a whole, i.e., aperiodically, like the transmitting and receiving discs of the telephone, and (b) those which assume that certain structures, probably the membranes, vibrate in parts, i.e., periodically, just as the various strings of a piano vibrate in sympathy with a corresponding note when the dampers are off.

Physiologists, however, are inclined to cling to the resonance or harp theory of Helmholtz. This theory is based on the assumption that the basilar membrane is composed of transverse fibers which increase regularly in length and thickness from the base of the cochlea to its apex. Each of these fibers is assumed to have its own vibration frequency, and therefore resonates when that particular frequency is a component of the vibration set up in the cochlear fluid. The organ of Corti in man is about 31.5 mm. in length and has three spiral turns, the basal turn being 18.2 mm., the middle 9.3 mm., and the apical 4.0 mm. That the organ of Corti does act as a resonator has been shown in experiments on fresh post-mortem human ears. A small manometer thrust into the organ at three different levels gave distinct resonance curves when tones of different pitches from a siren were sounded nearby, the frequency being higher the nearer the insertion of the manometer to the round window. Furthermore, upon destroying the apex of the cochlea in the dog and consequently the longer and thicker fibers of the basilar membrane, the animal no longer responds to notes of low vibration rate; or if the base of the cochlea is destroyed and with it the shorter and finer fibers of the basement membrane, there is inability to hear sounds of a high vibration rate. By means of delicate drills the organ of Corti of the guinea pig has been damaged at various points. Audiograms made of the electrical responses of the cochlea after the operation showed that lesions in the first turn of the spiral interfered with reception of tones of 4,000 vibrations and above; lesions in the second turn interfered with tones in the neighborhood of 2,000; lesions in the third turn interfered with those of about

1,000; and lesions in the fourth interfered with those from 32 to 500. The relative positions of these resonant areas for different pitches are the same for the human cochlea, although the latter has three turns only. It has been claimed that guinea pigs subjected to prolonged stimulation with very intense sounds of a given pitch become less sensitive to sounds of that pitch as tested by the method of conditioned reflexes, and that at post-mortem examination lesions are found in the cochlea, particularly degeneration of the external hair cells. It is somewhat disappointing for the place theory, however, to find that the newer methods of registration show that there is little correspondence between the deafness produced by continuous stimulation and the pitch of the tones used to produce this deafness. Tones of low frequency have no effect, while those above 2,500 cycles per second may produce impairment whose location in the frequency scale bears little, if any, relation to the stimulating pitches. Likewise the site of lesions produced in the cochlea under these conditions, as revealed by histological examination, is not so exact as one could wish. For pure tones and for detonations the severest histological changes occur in the middle portion of the cochlea and often both the range of pitches for which the animal is deaf and the cochlear lesions are widespread and not specific. Again, extremely delicate experiments in which only a very short length of the spiral ligament of the organ of Corti was detached from the bone, thereby loosening the tension on a very limited number of the basilar membrane fibers, have shown that tonal localization in the cochlea is none too exact, especially for low pitches. This may be related to the finding that the basilar membrane does not increase in width at all regularly as it passes from base to apex of the cochlea. It narrows and widens at odd intervals. In boiler-maker's disease, there is inability to hear notes of a high pitch, and post-mortem examination has shown that the short fibers of the basement membrane at the base of the cochlea have degenerated.

The part played by the basilar membrane has been examined by photographing the waves produced by the cochlear response. This membrane (in the cat) has a natural vibration rate of 800 to 1,000 per second, and apparently vibrates as a whole to tones below 1,000. To tones of higher pitch it vibrates for about 0.01 second at its own natural vibratory rate, then takes on the rate of the sounding body. Thus for tones of low pitch the membrane may act according to the "telephone" theory and for those of higher pitch according to the "place" theory.

The study of the mechanism of hearing has received great impetus from the discovery of the "Wever-Bray effect." When the auditory nerve of a cat was connected with a loud speaker and the amplified action currents set up by speaking into the cat's ear were recorded as sound, the quality of the speaker's voice and his very words were reproduced with great fidelity. Pure tones at pitches up to 20,000 vibrations per second were also faithfully reproduced. This phenomenon at first seemed to support the "telephone" theory since no known nerve had a refractory period sufficiently short to permit it to conduct impulses at these high rates. It is now found that two phenomena were intermingled in these first experiments: (1) a cochlear response, and (2) the eighth nerve response. Among the various theories proposed to account for the origin of cochlear potentials, two rival ones have strong adherents: (1) the membrane theory, which postulates that these potentials are generated by movements of fluids separated by a membrane, e.g., endolymph and perilymph separated by Reissner's membrane; and (2) the hair-cell theory, which postulates that they arise from activity in the hair cells of the organ of Corti. There is no doubt that movements of fluids and membranes can generate electrical potentials, but it is improbable that these would be large enough to account for the cochlear potentials. The chief argument for the hair-cell theory rests on the finding that albino cats, waltzing guinea pigs, and congenitally deaf Dalmatian dogs exhibit no cochlear potentials, and histological examination of their inner ears discloses complete absence of the organ of Corti with its hair cells. The threshold for these potentials of the cochlear response corresponds exactly with thresholds of hearing in the human ear. The eighth nerve response, because the refractory period of the nerve is approximately 0.001 second, can follow the frequency of stimulus only up to 1,000 per second. By rotation of activity of individual fibers the frequency of the stimulus may be reproduced up to 3,000 per second. Above 3,000 per second the response becomes irregular and the loud speaker gives forth a roar instead of the clear-cut tones of the cochlear response.

It is often difficult, however, to obtain pure nerve potentials without admixture of cochlear potentials. The two effects are distinguished from each other (1) by the longer latency of the nerve response, 0.5 msec. or more, as compared with 0.1 msec. or less for the cochlear response, (2) by the fact that the polarity of the cochlear response changes

with that of the sound waves, while that of the nerve response remains constant. Furthermore, the cochlear response is less susceptible to anesthesia, interference with blood supply, cold, etc., than the nerve response.

From these studies on the electrical responses of the acoustic system the conclusion seems warranted that the cochlear potentials represent the form in which the stimulus is received and modified by the peripheral mechanism of the ear; that the cochlea is an analyzer of sound, but that it has only a limited differentiation of response with respect to stimulus frequency, i.e., pitch; and that practically the whole basilar membrane is involved if a single tone possesses sufficient intensity. For frequencies below 1,000 cycles per second single nerve fibers of the auditory nerve can follow the stimulus frequency with fair fidelity; above that limit the stimulus frequency must be represented by the total pattern of volleys over numerous nerve fibers. Wever and Bray feel that these results cannot be adequately explained on the generally accepted "place" theory, and have therefore proposed a modification of it which they call the "resonance-volley" theory. According to this theory (1) pitch has a twofold representation, i.e., low tones are represented by frequency, high tones by place, and other tones by a combination of the two, (2) loudness is correlated with the total number of impulses passing over a nerve per unit of time, i.e., both the number of nerve fibers conducting volleys of nerve impulses and the rate at which impulses travel over them are involved. This latter concept brings intensity representation in the auditory nerve into line with intensity representation in cutaneous and other nerves, as shown by Adrian in his studies on the electrical responses of these nerves.

Deafness.—One can classify defective hearing as (1) transmission or conductive deafness, where there is interference with some part of the conducting system on the way to the inner ear; (2) perceptive deafness, where the organ of Corti or the auditory nerve is at fault; or (3) central deafness, where the lesion is in the central nervous system. The first two types are readily distinguished by Rinne's test.

A vibrating tuning fork is placed on the mastoid bone on the side of the ear to be tested—the other ear being blocked by the observer's finger—until it is no longer heard by bone conduction. The fork, still vibrating, is then quickly brought around to the opening of the external auditory meatus. A person with normal middle ear conduction will now perceive air-borne sounds of the fork for a short time after they have become inaudible through bone conduction, while a person with transmission deafness will not. The modern method of making quantitative auditory tests is by means of the audiometer, a machine in which both the pitch and the intensity of tones can be recorded accurately. Since loud tones are felt as well as heard, the audiogram shows a subject's thresholds both for feeling and for hearing. The threshold for hearing is lowest for tones about 2,700 cycles per second, involving an actual pressure variation of 1/12,000 bar,* an extremely low value indeed. For tones of 64 cycles per second, the lowest perceptible pitch, a pressure of 100 bars is necessary; and for tones of 20,000 cycles per second, the highest perceptible pitch, a pressure of 500 bars is required. The ear in its hearing capacity is therefore extraordinarily more sensitive (several million times more so) to tones of medium pitch than to those of high or low pitch near the limit of audibility. The threshold for feeling, on the contrary, is lowest for tones near the upper and lower limits of audibility, but highest for tones in a middle range in the neighborhood of 500 cycles per second. Pressure variations above 500 bars usually cause pain and may result in damage to the delicate structures in the ear.

*1 bar is a pressure of 1 dyne per sq. cm.

CHAPTER XXVI

CHEMICAL SENSES

Under the head of *chemical senses* come smell, taste, and the common chemical sense. The nature of the stimulus for these three senses is the same, but the degree of sensitivity of each is different. Smell is the most acute, that is, smaller amounts of a substance can be detected by its odor than by applying it to the tongue or to a mucous surface. The order of sensitivity of the olfactory organ can be compared to that of a chemical balance, the sensitivity of the gustatory organ to that of grocer's scales, and the sensitivity of mucous membranes to that of hay scales. Thus, a 0.000125 M solution of ethyl alcohol can be detected by its odor, a 3 M solution by its taste, and a 5 to 10 M solution by its stinging effect on the inside of the cheek.

SMELL

The olfactory organ lies in the upper part of the nasal cavity. The area innervated by each olfactory nerve would be approximately square in outline if spread out flat, and would measure not far from 25 mm. to a side. The color of this area is yellowish, while the respiratory epithelium is red. The olfactory cells resemble the sense cells of invertebrates, e. g., the bristle cells of the earthworm, and differ from the usual vertebrate epithelial sense cells in that fibers pass from them into the central nervous system. In other vertebrate sense organs the sensory cells have a synaptic relation with nerve fibers which have grown out from nerve cells located centrally. Protruding into the layer of mucus and lying over the surface of the cells are long hairs arising from the distal ends of the olfactory cells. These hairs are of extraordinary length; in the frog they may be 200 μ, and are of a lipoid nature. The fibers from the olfactory cells pass through the cribriform plate to terminate in the olfactory lobes in synaptic relation with the mitral cells. One mitral cell is connected with several sense cells so that the effect of a stimulus would appear to be reinforced by the reaction from several sense cells.

Odorous particles do not reach the olfactory area directly when a breath is taken, for various experiments show that air drawn in and out through the nostrils does not enter the olfactory chamber. Upon sawing the head of a cadaver in two and replacing the nasal septum by a glass plate, it is found that smoke blown through the nostrils does not enter this olfactory chamber. If a living subject breathes powdered magnesia and the distribution of this powder is determined by use of a rhinoscope, it is found that the particles have not entered the olfactory chamber. The odorous substances reach the olfactory cells through diffusion, hence there is a delay in the perception of an odor. There follows a reflex inspiration, rather short and vigorous, in fact a sniff, and the breath is held. This causes changing currents of air to be set up in the nasal chamber and the air just inspired being colder than the air inside causes convection currents and more rapid diffusion, and in this manner a greater concentration of the odorous particles reaches the olfactory epithelium.

Quantitative measurements of olfaction are possible by the so-called "blast injection test." A definite volume of air containing a known amount of a volatile substance is forced at a given pressure into one or both nostrils. The minimum number of cubic centimeters of an odor that can be identified when injected into both nostrils at once is called the *olfactory coefficient* of that

odorous substance. It is found that there is a direct relation between olfactory coefficient and boiling point. Thus the boiling point of turpentine is 158° C. and that of camphor 220° C.; the olfactory coefficient of turpentine is 10.7, and that of camphor is 14.9. Knowing the boiling points of two odorous substances and the olfactory coefficient of one, the coefficient of the other can be found from the simple proportion $b.p._1 : b.p._2 = coef._1 : coef._2$. A study of olfactory fatigue has been made by passing a continuous stream of air laden with odorous substance. It is found that fatigue for one odor is mainly specific, though there is some diminution in acuity of smell for other odors. By a combination of these two methods it has been possible to detect whether certain brain tumors were small or large and whether they were situated on the undersurface of the frontal lobes in such a way as to press upon the olfactory bulbs or tracts.[11]

Many classifications of odors have been made but none is really satisfactory. An attempt by Henning to construct an olfactory solid in the manner of the color solid lies perhaps nearer the truth than any of the others. He classifies the odors as: (1) flowery, e.g., violet; (2) fruity, e.g., lemon; (3) spicy, e.g., nutmeg; (4) resinous, e.g., frankincense; (5) putrid, e.g., hydrogen sulfide, (6) burning, e.g., tar. The olfactory solid is a five-sided prism, three of whose faces are squares, and the remaining two equilateral triangles. Diagonals, edges, and corners show the possible relations between odors; thus garlic is represented by the diagonal between spicy and putrid, fish scales between putrid and resinous, and vanilla between flowery and fruity.[13]

Earlier experimenters thought that the fifth nerve was also concerned with the sense of smell. Puppies in which the fifth nerve was cut no longer responded to tobacco smoke. The explanation was found later. Tobacco smoke is an irritant as well as an odorous substance, and the reactions of the puppies were to the irritating effect on the pain endings in the respiratory epithelium of the nasal chamber. Puppies with the first nerve cut were unable to find their food by sense of smell; while those with the fifth nerve cut had no difficulty.

Ellsberg has used quantitative olfactory tests as an aid in localizing brain tumors in the anterior fossa of the skull. If the olfactory tract or lobe on one side is involved, the olfactory coefficient is raised, or the sense of smell may be completely abolished.

TASTE

The sense of taste is associated with peculiar organs known as taste buds, which in man are found only in the oral cavity. Taste buds are found on the tongue except in the mid-dorsal region, on both the anterior and posterior surfaces of the epiglottis, on the inner surface of the arytenoid process of the larynx, on the soft palate above the uvula, on the anterior pillars of the fauces, and on the posterior wall of the pharynx. The distribution is greater during fetal life and in babes and young individuals than in adults. The center of taste shifts with growth of the individual from the tip of the tongue to a position in the neighborhood of the circumvallate papillae.

Unlike the olfactory cells, the taste cells are modified epithelial cells about which nerve fibers arborize. The nerves concerned are: (1) the seventh, which sends fibers from the geniculate ganglion through the chorda tympani to the lingual and thence to the anterior two-thirds of the tongue; (2) the ninth, which innervates the posterior third of the tongue, and (3) the tenth, which carries the impulses from other regions than the tongue possessed of taste buds. Cutting

the chorda tympani or the ninth nerve causes the taste buds to degenerate. In one person having a fistula in his ear it has been possible to stimulate the chorda tympani directly. Trials were made at different times and by different means of stimulation. The subject reported sensations of sweetness, sourness, saltiness, and bitterness only.

Action potentials appear in the cat's gustatory nerves in response to NaCl, HCl, quinine, and sucrose applied to its tongue, showing that taste buds even in the lower mammals respond to the same four categories of substances that are effective on the human tongue.

The methods employed to determine the thresholds of taste are (1) application of drops of solutions to the surface of the tongue or even to individual papillae; (2) taking 10 ml. of the solution into the mouth; (3) comparing 10 ml. of the solution with 10 ml. of distilled water; (4) sampling two solutions of different concentrations as often as desired. It is claimed that the last method gives the best results. For example, one can distinguish 0.01 per cent NaCl from distilled water, but cannot recognize the salty taste unless the concentration is raised several fold.

Qualitative tests show that the *sweet* taste is excited by alcohols, aldehydes, and ketones of the aliphatic series, and especially by hexoses and di- and polysaccharides. A few other substances, such as lead acetate (sugar of lead), saccharine, chloroform, etc., also arouse the sensation of sweetness. Several chemists have tried to show the relation between chemical structure and sweetness. The most acceptable theory is that there are two groups in every "sweet" molecule, a gluciphore, such as CH_2OH-CHOH, and an auxogluc, such as H-, CH_3, etc. Thus, glycerol HC_2OH CH_2OH-CH_2OH-CH_2OH is composed of the gluciphore CH_2OH-CHOH and the auxogluc CH_2OH. The tip of the tongue appears to be more sensitive to sweet substances than other parts.

A *salty* taste is aroused by application of the chlorides of potassium, lithium, ammonium, and magnesium; the bromides, iodides, sulfates, and nitrates of sodium and potassium. The taste is evidently due not to the whole molecule but to the anions. This is shown by the fact that a 0.04 M solution of NaCl is salty, while a corresponding solution of sodium acetate is not. A 0.04 M solution of potassium chloride, lithium chloride, and sodium bromide, all taste salty, and the same sensation is aroused by a 0.16 M solution of sodium iodide. The salty taste appears to be more concentrated on the tip of the tongue.

The *sour* taste is aroused by acids, but since one cannot distinguish between HCl, HNO_3, and H_2SO_4, the stimulus must be the hydrogen ion. Certain weak acids, such as acetic, are able to stimulate the tongue at lower concentrations of the hydrogen ion than stronger acids. The explanation is probably their greater power of penetration into living cells. It has been suggested that whole molecules of these weak acids may enter the cells and then dissociate inside the cell. This would mean that at a given molecular concentration more hydrogen ions would be acting on the cell from a weak acid than from a strong one. The sour taste is more easily detected on the borders of the tongue.

The *bitter* taste is characteristic of alkaloids and a series of unrelated substances like picric acid, Epsom salts, etc. It is more readily detected at the back of the tongue. Stimulation of individual papillae on the tongue has been carried out in a series of experiments on different individuals. The results show that some papillae respond exclusively to one or other of the four taste stimuli,

while others appear to be mixed. From this it is concluded that in reality taste is a composite of four separate senses, and that if not each papilla at least each taste bud contains a taste-receptive substance which is decomposed by the exciting substance to which it is sensitive. It is found that certain persons cannot perceive the bitter taste of para-ethoxy-phenyl-thio-urea and that this peculiar deficiency is inherited as a simple recessive.[45] The bitter taste of sodium dehydrocholate can be used in determining the rate of blood flow in man. The solution is injected into an arm vein and the time elapsing between the injection and the perception of a bitter taste is taken as the time for the blood to pass from the arm to the tongue. This reaction is especially interesting, as it shows that the taste buds can be stimulated by substances in the blood stream as well as by substances applied to the surface of the tongue.

Henning has constructed a taste solid in a manner similar to the odor prism. The taste solid is an equilateral and equiangular tetrahedron, with the four sensations sweet, salt, sour, and bitter at the four corners. Mixed sensations would be represented by points lying on the edges of the tetrahedron. Thus, lead acetate is both sweet and sour; acetone, both bitter and sweet; potassium sulfate, both sour and bitter; and magnesium chloride, both salt and bitter.

PART III

THE CIRCULATION

By H. C. Bazett*

CHAPTER XXVII

THE BLOOD

The blood is here considered as part of the circulation. The circulation exists to move the blood and to ensure the maintenance of normal conditions within it. The blood is of primary importance and the circulation the means to an end. The blood has so many essential functions, however, that its consideration enters into several sciences fundamental to medicine besides physiology. Many aspects of the subject will consequently be mentioned only in outline here or be neglected completely. They may be found treated in textbooks of histology, biochemistry, hematology, pathology, and immunology. Many of the properties of the blood which belong properly to physiology have such far-reaching correlations, that even they are more readily considered in their relation to other aspects of physiology. Thus the volume of the blood and its measurement is considered later in relation to fluid balance in the body as a whole. The carriage of oxygen and carbon dioxide is considered in relation to respiration, as is also the "buffer" activity of the blood whereby it assists in the maintenance of a stable degree of alkalinity. Variations in the chemical composition of the blood are discussed in relation to metabolism. Here, therefore, the general function of the blood will be considered in outline only. Some attention will be given to the formation and destruction of the blood cells but again only in outline. Blood coagulation with its profound medical importance and intimate concern with many physiological problems will receive more detailed treatment. The circulation of the blood will receive major attention. For other aspects of the subject the reader should consult other sources.

THE FUNCTION OF THE BLOOD

The blood is a very important element of the body and of its economy. In the process of evolution and development of complex multicellular animals it has proved essential for such organisms to maintain a more or less constant environment for their individual cells. This duty is undertaken by the blood, which replenishes the fluid surrounding the cells and ensures a composition of this fluid that varies only within narrow limits. As far as electrolytes are concerned the composition of the fluid is maintained at a level which probably resembles that of the primitive sea in which the early ancestors of the mammals developed. The function of the blood in maintaining this environment was originally emphasized by Claude Bernard, who developed the concept of

*Chapter XXVIII in this section has been written by Harry Eagle.

"le milieu intérieur." This idea has been more recently brilliantly developed by Cannon who draws attention to the essential constancy of the system by the term "homeostasis."[7]

This condition of homeostasis is achieved by the blood, which acts as a transporting mechanism, through the cooperation of other organs of the body, such as the respiratory system and the kidneys, which regulate blood composition. One may find many analogies between the industrial organizations of communities, and the organization of cellular activity in an individual. Thus the nervous system may be compared with a telephone exchange system. In such analogies the blood and circulation must be considered not only the railroad, but also the ventilation, drainage, and cooling systems. In addition, blood carries out the functions of the post office. It has also developed a self-sealing mechanism, blood coagulation, to prevent leakage from any damaged conduits. In this safeguard it long antedates the modern self-sealing inner tube. The more detailed and more scientific discussion of properties of blood given later should not be allowed to hide these essential functions.

THE COMPOSITION OF THE BLOOD

The blood consists of a suspension of cells of three types: nonnucleated red cells, the *erythrocytes,* white nucleated cells, the *leucocytes* and *thrombocytes.* The first contains hemoglobin and functions particularly in connection with the gas-carrying properties of the blood; the second is of importance in the scavenging and immunological activities of the blood; the third functions in blood coagulation. The corpuscles are suspended in a protein and salt solution known as the *plasma.* If blood clots, one of the plasma proteins (fibrinogen) is converted into an insoluble modification (fibrin), and the remaining fluid is then called blood *serum.*

The approximate composition of the blood of a normal man is given in Table VI. It should be understood that the composition is not by any means constant, yet blood as a whole is more remarkable for its constancy of composition than for its variations. Table VI gives the orders of magnitude commonly encountered, but no attempt is made to set the normal limits. It must be remembered that many of the values given are conventional. For instance, the grams of hemoglobin per 100 ml. of blood are expressed on the arbitrary assumption that 1 gram of hemoglobin can combine with 1.34 ml. of O_2. The accuracy of the ratio of oxygen to each atom of iron is not in doubt; the absolute relationship of oxygen to 1 gram of pure hemoglobin is less certain, and probably varies somewhat in different species.

The composition of the blood is not constant even in a single individual. It varies from moment to moment, and as will be seen later it may be modified by many physiological factors.

THE ERYTHROCYTES

The Structure of the Erythrocyte.—The normal erythrocyte in man is a biconcave disc with a transverse diameter averaging about 7.8 μ and a thickness (maximal) of 1.84 μ. The estimated volume of such a cell is 88 μ^3 and the surface area 140 μ^2.[15] The biconcave shape is one which supplies optimal conditions for interchange of gas, since it decreases the distances through

which the gases have to diffuse. Such a shape must be maintained by the opposition of two forces; one of these may be surface tension tending to give a spherical form, but the nature of the other is unknown. The cells are not rigid, but may assume varying shapes in their passage through the capillaries. The membrane probably consists of protein and lipoid material.

TABLE VI

COMPOSITION OF NORMAL HUMAN BLOOD

(Approximate mean values of some of the chief constituents compiled from Peters and Van Slyke,[30] Bürker,[6] and Adler.[1])

Specific gravity 1.050 to 1.065.

BLOOD PLASMA	PLASMA COMPOSITION	(GM. PER 100 ML.)
Male: 54% by volume.	Water	90.0
Female: 58% by volume.	Serum albumin	4.4
Specific gravity: 1.028 to 1.032	Serum globulin	2.3 } 2.6
	Fibrinogen	0.3 }
pH: 7.3 to 7.4 at 38° C.	Nonprotein nitrogen	0.036
	Glucose (apparent)	0.100
		(true 0.070)
	Chlorine	0.36
	HCO_3	0.18
	Phosphorus (inorganic)	0.003
	Phosphorus (other compounds)	0.020
	Sodium	0.335
	Potassium	0.02
	Calcium	0.01
	Magnesium	0.003

RED CELLS OR ERYTHROCYTES	RED CELL COMPOSITION	(GM. PER 100 ML.)
Male: 46% by volume.	Water	60.0
5,400,000 per c.mm.	Hemoglobin	32.0
Hb. 15.6 Gm. per 100 ml. blood.	Chlorine	0.18
O_2 capacity 20.9 ml. per 100 ml. blood.	HCO_3	0.09
Female: 42% by volume.	Potassium	0.42
4,900,000 cells per c.mm.		
Hb. 14.2 Gm. per 100 ml. blood.		
O_2 capacity 19.0 ml. per 100 ml. blood.		
Specific gravity of cells 1.082 to 1.102		

WHITE CELLS OR LEUCOCYTES	TYPES OF CELLS	% OF TOTAL	NO. PER C.MM.
6,000 per c.mm.	Polymorphonuclear neutrophils	67	4020
	Polymorphonuclear eosinophils	3	180
	Polymorphonuclear basophils	0.5	30
	Monocytes	7	420
	Lymphocytes	22.5	1350

PLATELETS OR THROMBOCYTES
234,000 per c.mm.

As can be seen in Table VI the composition of the red blood corpuscles differs considerably from that of the plasma. The erythrocytes contain a large quantity of hemoglobin which normally is not found in the plasma. Also in man and many animals the base present in the cells is mainly potassium whereas sodium is the chief base of the plasma. These differences in composition are

maintained by a membrane which, in the adult cell, is impermeable not only to protein but also to positively charged ions (cations). The membrane is permeable to anions and exchange of these negatively charged ions can occur across it. Thus Cl^- can be exchanged for OH^-.[22] Salt molecules as a whole cannot leave the intact cell, for the removal of an anion would leave a positive charge which would resist any further loss of anions. For this reason the salt content of the red cell exerts an effective osmotic pressure. If the cells are placed in water, the consequent entrance of water causes the cell to swell, until the membrane is so stretched that it becomes permeable not only to salts but also to hemoglobin. The hemoglobin escapes into the solution and the cell is said to have been *hemolyzed*. Since this depends on the swelling of the cell by osmotic forces, it is prevented if the water outside the cell contains an equivalent amount of salt which is unable to penetrate the membrane. The forces, which determine diffusion of water, are then equal on each side of the membrane and no swelling occurs. Usually a solution of sodium chloride is used, one greater in concentration than the sodium chloride of blood plasma but equivalent in osmotic pressure to the total electrolytes. Thus a 0.9 per cent solution of NaCl may be used; often a M/6 solution of NaCl (i.e., one of about 0.97 per cent) is employed. In these solutions the red cells are stable. Such a solution is called *isotonic*. In more concentrated solutions of salt the osmotic pressure outside the cells exceeds that inside, water passes from the cells to the exterior and the cells shrink. Such a solution is a *hypertonic* solution.

Hypotonic Hemolysis.—When the red cells are immersed in water or in a solution of salt of a molecular concentration less than that of a 0.9 per cent solution of NaCl, the cells absorb water and swell. Such a solution is called a *hypotonic* solution. In the process of swelling the cell becomes larger in volume but its greatest diameter (width) is reduced. It becomes more spherical. Thus the cell increases in volume without any increase in the surface of the envelope. It has been suggested by Ponder that the cell envelopes are not readily stretched beyond their original size without losing their impermeability to hemoglobin and salts. If the forces are such as to stretch the membrane beyond this value, complete hemolysis occurs. Such relationships have been found by Haden[15] to hold for human corpuscles. The shape, size, and volume of the normal erythrocyte and the surface area of its envelope are indicated in Fig. 97, *a*. The dimensions of a hypothetical spherical cell of the same volume are indicated in Fig. 97, *b*, and of a hypothetical spherical cell of the same surface area in Fig. 97, *c*. It will be noted that were the membrane spherical in shape it could theoretically hold a volume 70 per cent greater than that of a cell of normal shape. In Fig. 97, *d*, *e*, and *f* some examples of observed changes in shape during swelling in a hypotonic solution are shown. Some hemolysis begins to develop at stage *f*.

The capacity of a red blood corpuscle to swell and become permeable in a hypotonic solution has proved of clinical interest. In a population of red corpuscles the sizes, and probably also the shapes, of the individual cells vary.

In a normal blood usually no detectable hemolysis occurs in a solution of 0.48 per cent NaCl; the cells are merely swollen. In a solution of 0.32 per cent NaCl all the cells are hemolyzed. Between these limits some cells are completely hemolyzed, some cells are merely swollen, and some probably undergo a partial leakage of the cell contents. The distribution of these various types of reaction follows that to be expected on mere chance; it may be represented by a proba-

bility curve. In abnormal bloods the cells may be more spherical than normal. Their membranes are then smaller, and less swelling can occur before hemolysis develops. They hemolyze at salt concentrations greater than normal. The same result may be obtained if the walls become more readily permeable to hemoglobin. Such changes are seen in certain hemolytic anemias. On the other hand, the red cells which are thrown into circulation after repeated hemorrhages are commonly smaller and flatter than normal. They are more than normally resistant to hypotonic solutions. This may be due simply to their size and shape. Obviously the same effect would be found if the cell when swollen had its capacity to retain its electrolytes reduced more than its capacity to retain hemoglobin. Whether such a change can develop is not known.

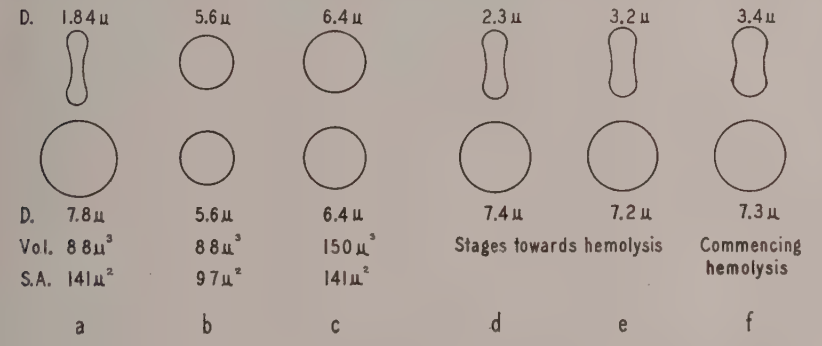


Fig. 97.—In *a* the normal shape of an erythrocyte in two planes is indicated; the diameter (D.), volume (Vol.), and surface area (S.A.) of such a cell are indicated. *b* represents the size of a spherical cell of the same volume as *a*, and c one with the same surface area as *a*. *d*, *e*, and *f* represent stages preceding hemolysis, as cells swell in hypotonic solutions. Some hemolysis of some of the cells occurs at stage *f*. (After Haden[15]).

The conditions are somewhat more complex when red cells are immersed in an isotonic solution of a substance which can penetrate the cell membrane more or less freely. Thus a M/3 solution of urea is isotonic with the red cell contents, but the urea is uncharged and can readily penetrate the cell membrane. Sooner or later, therefore, the urea will attain the same concentration inside and outside the cell, leaving the osmotic effect of the electrolytes within the cell unbalanced. Water ultimately enters the cell just as it would if the cell were immersed in pure water, and hemolysis occurs. The rate of development of hemolysis serves as a measure of the rate of penetration of the urea. The study of the kinetics of such processes has thrown much light on the laws governing permeability and on the properties of the membranes of red blood corpuscles of various species (Jacobs et al.[20-25]).

One of the substances that can penetrate the cell, though it is an electrolyte, is ammonium chloride. This also has been much studied. Cells immersed in M/6 ammonium chloride are hemolyzed and this hemolysis must be a hypotonic phenomenon, for addition of NaCl to the solution to a value of 0.9 per cent prevents it. The Cl^- ion can be freely exchanged with other anions. In a solution of this combination of chloride with a weak base some ammonium hydrate and some ammonia gas are also present. The ammonia gas, but not the NH_4^+ ion, can penetrate the cell. Within the cell the ammonium and Cl^- are capable of re-

combination. Consequently, the cell is permeated by such a substance. For this reason NH_4Cl in the solution outside a red cell can only delay, not prevent, hypotonic hemolysis. The probable interactions concerned are represented in Fig. 98.

The volumes of red cells do not remain constant in the blood stream. When blood gives up oxygen and combines with carbon dioxide, the osmotic forces within the cells are altered, water is absorbed, and the cells swell. A molecule of hemoglobin acts as a polyvalent ion combining with many atoms of base. Let us assume that it combines with n atoms of base (in human blood this is potassium). Then the total number of ions that result if the compound is completely ionized is $n + 1$ (n ions of K^+ and 1 polyvalent ion of hemoglobin). When carbon dioxide enters the cell, HCO_3^- ions are increased, and these compete with the hemoglobin for the available base. Let us suppose that all the base previously combined with the hemoglobin molecule is now combined with HCO_3^-. The number of ions is then $2n$ (n ions of K^+ and n ions of HCO_3^-). The value $2n$ always exceeds $n + 1$, if n is greater than 1. Consequently, the number of osmotically active particles within the cell is increased in venous blood. The volumes of red cells are therefore greater. The cells also swell to a greater extent in any given hypotonic solution of salt.

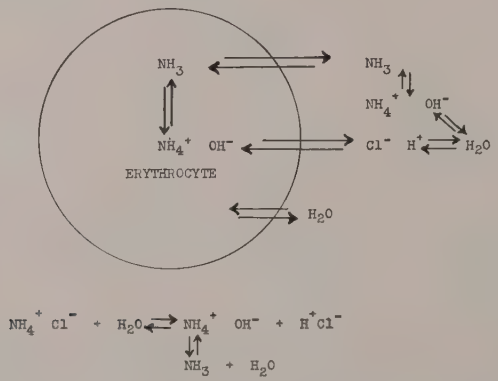


Fig. 98.—Probable relationships of exchanges between a solution of NH_4Cl and an erythrocyte.

In whole blood the forces are somewhat modified by similar changes in the plasma. Plasma protein also liberates base to combine with HCO_3^- but the change is less than that in the corpuscles. The picture is complicated also by changes in pH which are greater within the cell than within the plasma and by an exchange of HCO_3^- ions for Cl- ions between the cells and the plasma.

Similar changes in the osmotic forces within the cell result from alterations in pH and in temperature. The complicated effects have been brilliantly analyzed by Jacobs.[23] The temperature and the pH modify not only the rate of change but also the final point of equilibrium. For this reason, if accuracy is to be attained in hemolytic tests, both acidity and temperature must be carefully controlled. The effect of temperature depends partly on alterations in the capacity of proteins to combine with base, in the dissociation of water and other substances, and in a consequent considerable change in the pH of the blood.

The reader may here be reminded merely that the values for mammalian blood commonly dealt with both in biochemistry and in physiology are those observed at a tempera-

ture of 37° to 38° C., and that they are true only if the temperature is maintained constant. They are, therefore, only theoretical abstractions and first approximations of the truth, since the metabolic activities of the body are associated with heat production, and thermal stability is by no means absolute. In this connection it may be noted that the work of Austin[3] has shown that in the cold-blooded animal and probably also in the warm-blooded animal, the adjustments are such as to maintain relatively constant over a wide temperature range the base bound by protein which will in turn similarly maintain constant the electrolyte concentration and osmotic pressure. Such adjustments by no means leave the pH level constant, and any conception of the uniformity of the pH level must be limited to conditions in which the temperature is *assumed* to be constant. At constant CO_2 content human blood shows an increase in pH of about 0.014 unit for each degree C. fall in temperature.[38] When cooled in saline, the cellular contents show similar changes as the result of a decrease in the amount of base bound by protein; this alters their osmotic properties (in whole blood similar osmotic changes are progressing in the plasma surrounding the cells) so that at any critical concentration of NaCl a larger number of corpuscles are hemolyzed at a low temperature than at a higher one.[23]

Hemolysis may occur from causes other than changes in osmotic pressure. Substances, such as saponin, may modify or destroy the cell envelope, so as to make it permeable to hemoglobin and the other cell contents. It is probably through an action of this sort that the immune hemolysins, and hemolysins of bacterial origin, produce their effects.

The Sedimentation of Red Blood Cells.*—If blood is drawn into an anticoagulant, such as citrate, oxalate, or heparin, and is then placed in a tube, the red cells slowly settle out under the influence of gravity, leaving a supernatant layer of clear plasma. In many conditions, notably tuberculosis and pregnancy, the rate of this sedimentation may be enormously increased. Animal species also differ in their sedimenting activity. Thus, horse blood sediments so rapidly that the red cells often form a sharply demarcated layer at the bottom of the container even before coagulation occurs. The wide variations in the rate of red cell sedimentation depend primarily on differences in the rate and degree of *rouleaux* formation. Red blood cells in plasma aggregate to form neatly piled cylindrical stacks of cells, or rouleaux. In general, given a difference in specific gravity between a particle and the suspending fluid, the velocity with which that particle sinks will vary as the square of its radius. It is obvious that the larger the rouleaux, and the more rapid their formation, the greater will be the sedimenting velocity of the red blood cells. In some bloods, the cells clump very slowly, and the average number of cells per rouleau is small; these are the bloods which sediment slowly. In rapidly sedimenting bloods, however, the red cells begin to clump almost instantaneously, and eventually form cylindrical stacks containing twenty to forty cells. These adhere to similar rouleaux to form large clumps which under favorable circumstances are visible to the naked eye.

The other factors which affect the sedimentation rate, such as red cell count, or the viscosity of the plasma, are of secondary importance. The problem of sedimentation is essentially the problem of rouleaux formation, but the forces which cause this peculiar oriented aggregation of red cells are still largely unknown.

Rouleaux formation normally occurs in the circulating blood (Ploman) and is freely reversible. The formed cylinders redisperse on mild agitation, or on resuspension in salt solution. The activity is associated with the plasma;

*This section on Sedimentation is by Harry Eagle.

the cells play a purely passive role. Any suspension of human cells placed in an actively sedimenting human plasma will sediment rapidly; conversely, any cell suspension will sediment slowly in a normal plasma. The reactive factor in the plasma, whatever it may be, is rapidly destroyed by trypsin, and by small concentrations of acid or alkali ($<$ ph 4, or $>$ pH 9). It has been suggested that fibrinogen adsorbed by the cells causes their surface to become "sticky," and that the increased sedimentation (rouleaux formation) observed in various pathological conditions is due to an increased fibrinogen content of the plasma (cf. Fahraeus[12]). An increased globulin content and an increased globulin-albumin ratio have also been held to be the cause.

Perhaps the best working hypothesis on which to base an explanation of the mechanism of rouleaux formation and the resultant accelerated sedimentation is the one suggested by Fahraeus.[12] It is that an unidentified substance in plasma, associated with the plasma globulin, but tending to precipitate out with the most labile fraction (fibrinogen and euglobulin), increases the surface tension between the cells and the plasma. Under its influence the cells aggregate in such a fashion that they expose a minimal surface to the surrounding fluid. Given a suspension of discs, it is obvious that the minimum surface per unit volume would be represented by a cylindrical pile; this is the shape actually assumed by corpuscles in rouleaux. The free reversibility of the aggregation and the absence of demonstrable combination are entirely in keeping with this hypothesis.

Specific Characters of Red Cells; Agglutination Reactions

The specificity of red cells must be briefly outlined. Although the theoretical aspects of this subject lie in the field of immunology, it has great practical importance in the treatment of hemorrhage by transfusion.[10, 42] Transfusion has long been a subject of experiment and was attracting attention at the time of the foundation of the Royal Society of London nearly three hundred years ago. The earliest recorded experiment was performed by Richard Lower and one of the earliest by Sir Christopher Wren. It proved an unsatisfactory procedure, not only when blood from animals was transfused into man, but also when human blood was used. In 1900 Landsteiner, prompted by the discovery of serological specificity, set out to determine whether differences might not exist within the same species, and on this work is based our knowledge of the separation of human blood into different groups. Some of the more recent major advances in the field must also be credited to Landsteiner.

It has been demonstrated that human blood may be grouped into four types, which differ from one another not only in the characteristics of their red cells but also in those of their plasmas. The plasmas of some of these groups are able to make the red blood cells of others mass together into large clumps, i.e., to agglutinate them, and this change may be merely the initial stage of an actual hemolysis. One of the groups, the one most commonly found in Anglo-Saxon communities, possesses cells which are not agglutinated either by plasmas of other members of its own group, or by those of any other group; these cells are called O, and the group is termed the O group. Plasma (or serum) from members of this group is, however, able to agglutinate the cells of an individual belonging to any other group. There are also found in Anglo-Saxon communities numerous individuals whose cells are agglutinated by the plasmas of the O group, but whose plasmas, although unable to agglutinate the cells of that

group, do agglutinate the cells of a third group of individuals who occur more rarely in such communities. The second group is given the symbol A; their cells are called A cells and are said to have an agglutinable substance A (called usually, in defiance of accurate scientific terminology, an agglutinogen); their plasma contains an agglutinin which acts on the cells of the third group and is given the symbol β. The third group, rarer in the population under discussion, has cells which, like those of all other groups, is agglutinated by O plasma; they are also agglutinated by A plasma with its β agglutinin. It is given the term B and its cells and agglutinable substance are labelled B. The plasma of this group is found to have an agglutinin which can clump A cells, and it is said, therefore, to have an α agglutinin. It can be shown that the plasma of an individual of the O group, which is able to agglutinate both A and B cells, loses its capacity to agglutinate A, while retaining its ability to agglutinate B, if it be shaken with an excess of A cells and then centrifuged. Similarly, an excess of B cells may remove the capacity of acting on B cells. The O plasma is then in reality merely a plasma containing both α and β agglutinins. It is obvious that if the O cells were susceptible to these agglutinins, intravascular clumping and blocking of the capillaries would result.

Table VII

SERUM OR PLASMA		RED BLOOD CELLS				
GROUP	AGGLUTININS PRESENT	GROUP O	GROUP A	GROUP B	GROUP AB	% OF GROUPS IN ANGLO-SAXON COMMUNITIES
O	α and β	−	+	+	+	45
A	β	−	−	+	+	42
B	α	−	+	−	+	10
AB	−	−	−	−	−	3

+ indicates agglutination; − absence of agglutination.

With this information it became possible to discover the fourth and most rare group. In this the individuals have cells with agglutinable substances A and B, and have, consequently, a plasma free of both agglutinins α and β. This group is known as AB. The reactions of the four groups with one another may now be set out in tabular form. It will be noted that if either an A or a B blood is available, any other blood may be identified by its reactions to that blood provided both cells and plasma of each blood are tested; or, if both A and B plasmas are available, identification of any blood from the red cells alone is possible; lastly, if even a small number of blood samples are available (even 20), and the population is of Anglo-Saxon (or European) ancestry, the statistical chances of being able to identify the groups correctly by comparing the blood samples with one another is high. (This makes an ideal method for class study.)

Technical Methods.—The simplest and commonest method is to mix a minute amount of the cells to be tested with an excess of the citrated plasma or serum on a slide and to allow it to stand a few minutes. The massing of the corpuscles together may be readily seen by the naked eye. Occasionally agglutination is delayed and the slow commencement is then more easily determined under a microscope. If the delay is long, drying complicates the issue and for this reason some weak positive reactions may be missed. An alternative method is to use 1 drop each of serum, cell suspension, and saline in a small test tube of 7 mm. diameter. The mixture is allowed to stand one hour; a sample is then examined under the microscope. Low temperatures should be avoided, as nonspecific agglutinins acting

only in the cold, and sometimes even affecting corpuscles of the same blood, may be present. Usually tests are made at room temperature, but this should not be abnormally low. The agglutinable substances develop during antenatal life but do not reach their full development till about the age of twenty; the agglutinins have a similar development but are less developed in the earlier years of life.

Nomenclature.—In the historical development of our knowledge of agglutination much work was done in America by Moss, and in Europe by Jansky. The work of these men resulted in the groups being given numbers. The group here described as A was given the number II, and that described as B was called III in both systems. Group O was called I in the Jansky system and IV in that of Moss; group AB was called IV in the Jansky and I in the Moss classification. The Moss classification is still used in some English and American hospitals.

Subgroups of A.—Group A may be subdivided further into groups A_1 and A_2. There are apparently two α agglutinins, one α which reacts with all A groups, and the other α_1 which reacts only with the more common cells of type A, known as A_1. If cells known to be A_2 are available, a group O or B serum may be shaken with an excess of these cells, and later the serum separated. It will then contain only α_1 and react only with A_1 cells. Only some 28 per cent of B or O sera gives active remainders of agglutinin α_1. Similarly AB groups may be divided in A_1B and A_2B. Some believe the differences between these two subgroups to be merely quantitative and not qualitative.

Other Groups.—Additional specific differences exist. If a large number of cross agglutinations are made, rarely but definitely one may find an individual who reacts consistently as an O group in numerous tests, but is found to have his cells agglutinated by some member of another group, such as A_1, or even by a member of his own group O. Similarly with other groups. Often these abnormal agglutinations are of the nonspecific cold agglutinin type but not always. They are very rarely demonstrated, in that an abnormal agglutinable substance will not be detected unless it is mixed with a plasma which happens to contain the corresponding abnormal agglutinin. They are not detectable by the common clinical tests. It is for such reasons that it is important to make *crossed* agglutination tests, whenever possible before transfusion; in such tests the cells of each subject are tested with the other's serum.

The dangers arising from an incompatible blood are slight, provided that the plasma of the recipient is unable to agglutinate the corpuscles of the donor. If the plasma of the donor can agglutinate the corpuscles of the recipient, little effect may be produced even with a transfusion of 800 ml. of blood. The donor's plasma is so diluted by the recipient's blood that the agglutination reaction is weak or absent. On the other hand, the recipient's plasma is in excess and can exert its full effect on the donor's cells. For this reason blood from a subject of Group O (Jansky I or Moss IV) can usually be used safely in an emergency to transfuse subjects of any group. These subjects are consequently called "universal donors." Similarly, members of Group AB are known as "universal recipients." Occasionally a transfusion without any tests may be warranted in an extreme emergency, if due care is taken to watch for indications of incompatibility. The chances of a bad reaction are only about 3 in 10, since there is a reasonable chance that both donor and recipient belong to Group A and there is a 45 per cent chance that the donor belongs to Group O.

The agglutination of corpuscles precedes changes in the cell membrane leading to hemolysis. Where agglutination is seen hemolysis is likely to develop later. No exact parallelism between the degree of agglutination and the degree of hemolysis is found by methods at present in use.

In addition to such groups consistent differences between subjects are found in relation to the agglutinins developed in rabbits after injection with human blood. These properties are known as M and N, and are agglutinable substances capable of acting as antigens and inducing the formation of agglutinins in rabbits.

Hereditary and Medicolegal Aspects.—The inheritance of the groups is definitely established and follows Mendelian laws; it is, therefore, a valuable instrument in establishing whether a certain paternity is possible or impossible. Members of Group O are genetically pure, for O is a recessive characteristic; individuals of Groups A and B may have the genetic constitution of AA or AR, BB or BR, where R is is the recessive characteristic found in Group O as RR. Analysis of the data by Bernstein has shown that the behavior is that

of a triple allelomorph in which 3 genes A, B, and R may exist but only one at a time in a single locus in the chromosome. Each germ cell can contain, therefore, only one of these three genes A, B, or R, and, therefore, in the fertilized ovum the following genotypes are possible; homozygous AA, BB, and RR and heterozygous AR, BR, and AB. The possibilities of the various combinations can thus be deduced. More accurately the presence of subgroups A_1 and A_2 probably implies the existence of four allelomorphic genes A_1, A_2, B, and R in which A_1 is dominant over A_2. The factors M and N are transmitted probably by a separate pair of allelomorphic genes, with genetic possibilities of MM, MN, and NN. In a case of disputed parentage, by the use of these agglutination reactions and their Mendelian inheritance, there is, on the average, a 30 per cent chance of showing that a wrongly accused individual is not the father of a given child; with some combinations the chance of such proof is as low as 7 per cent, with others as high as 64 per cent. For details Wiener's monograph[42] may be consulted.

Anthropological Aspects.—The groups raise points of considerable anthropological interest. The pure American Indian, except for one or two tribes, appears to belong always to the O group; the A group is common in Europe, but among the inhabitants of North India (Hindus) the B group reaches a frequency as high as 41 per cent and the A group is relatively rare. The subject is further complicated by the presence also in apes of Groups O, A, B, and AB. The relationship of the group distribution to racial contacts is discussed by Wiener.[42]

Color Indices

Since the hemoglobin is contained in the red corpuscles there are relatively constant ratios between the hemoglobin concentration and the number and volumes of red cells present. The hemoglobin concentration may be determined by the capacity of blood to combine with oxygen or by its capacity to combine with carbon monoxide. Under ordinary living conditions the blood of normal city inhabitants, particularly if they are tobacco smokers, is apt to contain 0.2 or 0.5 ml. or more of carbon monoxide per 100 ml. of blood. It is difficult to get rid of this source of error in determining the hemoglobin concentration by measuring the oxygen capacity. The hemoglobin concentration may also be determined colorimetrically by various methods: the standards are set by one of the gaseous methods. The cells may be counted in a chamber under a microscope after appropriate dilution of the blood. The volume occupied by the red corpuscles may be determined by high-speed centrifugation in small capillary tubes. Such "hematocrit" values are given as the percentage of the total volume that is occupied by the red corpuscles. Since the size of the cells varies with physiological conditions such as the degree of venosity, the ratio of hemoglobin concentration to cell volume is not an absolute constant even in the same individual. Since the size of the cells and the hemoglobin contained per cell vary, particularly in disease, the ratio of hemoglobin concentration to the cell count varies from individual to individual. These variations are valuable in diagnosis.

The *color index* is used to indicate the ratio of hemoglobin content to the cell count. It is a measure of the hemoglobin content of each cell. The value of

$$\frac{\text{oxygen capacity in ml. of } O_2 \text{ combined per 100 ml. of blood} \times 0.26}{\text{million cells per c.mm.}}$$

gives this color-count ratio or color index.[30] The normal value is 1. A value above 1 indicates a hemoglobin content per cell above the normal (usually implying abnormally large cells); a value below 1 indicates a subnormal content of hemoglobin in the cells.

The ratio of hemoglobin to red cell volume is a similar comparison. It is found from the volume of the red cells as determined by the hematocrit. The ratio,

$$\frac{\text{oxygen capacity in ml. of } O_2 \text{ per 100 ml.} \times 2.2}{\text{volumes per cent of cells by hematocrit}}$$

gives the color-volume index again with 1 the normal value.[30]

THE FORMATION AND DESTRUCTION OF ERYTHROCYTES

The Life-Cycle of the Erythrocytes.—The survival period of erythrocytes in dogs seems to be clearly established by work from Whipple's laboratory.[16] When red corpuscles are destroyed, the iron is mainly retained for future use while bile pigment is formed from the porphyrin element of the hemoglobin molecule and is excreted. The rate of formation of bile pigment can therefore serve as a measure of cell destruction. It is difficult to estimate this rate accurately if the bile is delivered into the intestine. Accurate estimates may be made if the common bile duct is obstructed, and the bile is drained from the gall bladder through a fistula. The basic level of bile-pigment formation may thus be determined. If the total circulating hemoglobin be reduced by bleeding to about a quarter of the normal level, the normal level of hemoglobin in the blood is regained in about two weeks. The larger proportion of the circulating cells are then young cells, just commencing their normal life. The level of bile-pigment excretion falls, and remains below normal. About four months later the bile-pigment excretion suddenly rises above the normal value. This indicates that the numerous red cells formed to compensate for the loss by hemorrhage have suddenly and contemporaneously reached the limit of their survival time. From such data the average survival time for erythrocytes in the dog is estimated as about 120 days.

The survival of human corpuscles has been determined by the duration of survival of cells of type O injected into an individual of another type. Some observers have obtained values as long as 120 days, but the data secured in this way have been very variable. One may assume a duration of corpuscle life in man similar to that observed in the dog. A man of average size may have a blood volume of about 5.9 liters (Chap. LXXVIII) containing about 900 grams of hemoglobin. Therefore the daily destruction of corpuscles should be normally $\frac{900}{120}$ or 7.5 grams a day. This would entail the formation of 280 mg. of bilirubin daily from the destruction of about 20 ml. of red blood corpuscles, and it implies that a similar volume of young cells is added daily to the circulating blood.

Formation of Erythrocytes.—The erythrocytes are formed in the early embryo from primitive mesenchyme cells which develop to form both blood corpuscles and the walls of the vessels. Later in embryonic life the formation of red cells occurs in a similar way but it is limited to bone marrow, spleen, liver, and lymph glands. In the adult it is normally limited to the bone marrow, but under stress the spleen can apparently regain the capacity of forming red blood corpuscles that it had in embryonic life. In the adult the red corpuscles are formed from primitive blast cells which develop through the following stages: megaloblast, a large nucleated cell commencing to develop a hemoglobin content; macronormoblasts, similar but nonnucleated cells which

are basophilic; normoblasts, smaller cells also nonnucleated and eosinophilic; reticulocytes, young red cells with a network staining with basic dyes; fully developed red corpuscles.[19, 33, 34] About 1 to 3 per cent of the cells in the normal circulation are in the reticulocyte stage. A larger proportion of these cells are found during periods of increased cell formation. The nature of the reticulum is not known. It may consist of protoporphyrin which is found in reticulocytes but not in adult red corpuscles.[39]

The red corpuscles develop in the red bone marrow in sinusoidal vessels which form a closed system with the rest of the vascular bed. The red cells are developed from the cells lining these vessels. During the growth of the red cells the whole vessel appears to be blocked off from the main circulation by constriction of the connecting channels. These vessels apparently open up and allow release of the corpuscles when the cells become mature. With increased formation of red blood corpuscles, as after hemorrhage, the red bone marrow spreads in the long bones replacing fatty yellow marrow. The increased growth of the red marrow is apparently induced by a decreased oxygen supply, however this decrease may be brought about. A reduction in the hemoglobin content or in the oxygen saturation of the circulating blood may be the cause, or a reduction in blood supply whether induced reflexly from receptors, such as the carotid sinus or carotid body,[27] or by some organic interference with the blood vessels to the bone marrow.[31] Red bone marrow and red corpuscles do not develop in the more peripheral bones. This fact appears to be due to the lower temperatures that prevail in such peripheral tissues. For instance, red bone marrow does not develop in the tail vertebrae of rats, but if these bones are kept warmer by grafting the tail in the abdominal cavity, they form red bone marrow.[18]

Certain substances are essential as materials for the formation of red corpuscles, others seem to be necessary for the process of development. *Iron* is combined with a porphyrin to form heme, and this combines with a protein to form hemoglobin. Iron is essential to blood formation. It is conserved in the body when red blood corpuscles are destroyed, so that there is little loss of iron except from hemorrhage. The growing child needs a supply of iron, since the iron-containing tissues are being increased. The adult man requires only traces of iron unless he loses blood by hemorrhage. The adult woman, on the other hand, requires an intake of about 0.3 gram per year since there is normally a loss through menstrual bleeding. Nearly twice this is needed when menstrual losses and growth needs are both factors.[17] Obviously individual requirements must vary considerably.

The normal individual may be considered as having a blood volume of 5 to 6 liters with a circulating red cell volume of 2 to 3 liters, and a total hemoglobin of 700 to 900 grams. The latter values imply an iron content of the circulating blood of 2.4 to 3.0 grams. Additional iron is present in the tissues in myohemoglobins, cytochromes, etc., to the extent of about 0.3 gram. The bone marrow is estimated to have a volume of about 1.4 liters. Additional iron is contained in hemoglobin in the bone marrow and in red corpuscles temporarily side-tracked in the spleen as well as in substances resulting from red cell destruction. Such additional reserve supplies of iron amount to about 1.3 grams. The total iron in the body is thus of the order of 4 to 5 grams.[17]

The iron required to replace that lost through hemorrhage is not readily absorbed from the intestine. A considerable amount of iron may be taken in

the food in the form of heme, as cytochromes, etc., but this does not appear available for blood cell formation. Inorganic iron in the ferrous state appears to be used. Only a very small proportion of the inorganic iron of the food is absorbed from the intestine. A daily intake of 15 mg. of iron is considered optimal, i.e., an intestinal intake more than 15 times the actual requirements of an adult woman for cell replacement. Copper does not enter into the formation of hemoglobin, but it seems to act as a catalyst in this formation and traces of copper are thought to be essential. Traces of cobalt seem to have a similar action.[36]

The porphyrin part of the molecule is formed readily. Neither chlorophyll nor heme compounds in the food appear to affect hemoglobin formation. On the other hand, the protein globin is not readily formed except from suitable precursors. Among amino acids histidine and phenylalanine are important. Among protein foods liver stands highest; kidney, spleen, pancreas, and some fruits (apricots, peaches, and prunes) stand high, while dairy products, fish and other sea food are relatively inert.[41] The vitamin riboflavin has a definitely favorable, but probably not a specific, effect on hemoglobin production.[14]

There is no doubt that products from broken-down red cells are utilized in the regeneration of new corpuscles. The effect of hemorrhage in causing red cell production has been mentioned in discussing the life cycle of the erythrocyte. Actually better results are obtained in such experiments if red cell destruction in the body is produced by the drug acetyl-phenyl-hydrazine. Essential products of the cell destruction are then retained in the body and new cell formation is more readily attained. The products retained undoubtedly include the iron, and probably also parts of the globin fraction.

The study of anemias has thrown considerable light on cell formation. In anemia due to repeated hemorrhages, where the supply of iron and other materials may be low, new red cells are commonly small and contain a subnormal amount of hemoglobin. The color index is low. In pernicious anemia, on the other hand, the color index is above 1, even though the hemoglobin percentage is subnormal. The hemoglobin per cell is high. This depends on the presence in the circulating blood of abnormally large cells known as macrocytes, due to a failure of the developing red cell to attain proper development in the megaloblastic stage. The discovery by Minot of the specific effect of liver therapy in pernicious anemia demonstrated that the liver contains something which enables the numerous megaloblastic cells present in the bone marrow to develop normally. Liver treatment of such patients not only increases the number of cells, but also floods the blood with normal reticulocytes, which appear in numbers more or less proportional to the previous anemia. Extracts of liver in 70 per cent alcohol are effective in these cases, but not in anemias of other origin. The patients have a deficiency of an active liver substance which can withstand boiling. Achlorhydria (low or absent HCl in the gastric juice) is also an invariable accompaniment of pernicious anemia. The work of Castle[8] demonstrated that patients with pernicious anemia are deficient in a substance formed in the stomach known as the *intrinsic factor*. The intrinsic factor acting on another factor, the *extrinsic factor,* which is derived from certain foods, including beef muscle, produces the active liver substance. A precursor of the active substance is thus formed in the intestine, is absorbed and modified; the modified substance is that stored in the liver. Hydrolysis of liver extracts with dilute sulfuric acid destroys the active substance and

liberates the extrinsic factor. The extrinsic factor also resists heat in an autoclave. It is soluble in 80 per cent alcohol. It was thought at one time to be the vitamin B_2, but this does not appear to be the case. The intrinsic factor seems to be a product of the pyloric glands of the stomach, and of Brunner's glands in the duodenum.[29] It is not hydrochloric acid, pepsin, rennin, or lipase. It does not withstand boiling. Though achlorhydria is found in pernicious anemia, the reverse statement is not true; pernicious anemia need not result from achlorhydria. Much further study will be required before the parts played by the various factors mentioned are fully understood.

The Destruction of Erythrocytes.—Erythrocytes in circulation become damaged; probably the older cells are the more susceptible. The damage appears to be due to the stresses sustained by the cells in passing through fine capillaries, particularly in active muscles. There is evidence that in animals heavy muscular work is associated with an increased destruction of corpuscles, and such work may at first cause a reduction in the total circulating hemoglobin. It is probable that some of the cells undergo fragmentation within the vessels. The damaged cells or their fragments are taken up by phagocytic cells of the reticulo-endothelial system.[11, 32, 35] This process is carried on in bone marrow, spleen, liver, and hemolymph glands as well as by the phagocytic histiocytes found generally in connective tissue. The spleen, hemolymph glands, and bone marrow are the most important sites of destruction. Within the phagocytic cells the hemoglobin is broken down to its constituents, globin and heme. The latter is further split into the iron-free pigment hematoidin, which becomes the bilirubin of the plasma, and hemosiderin, in which form the iron is stored until it is needed for new hemoglobin synthesis. The bilirubin is excreted by the liver in the bile. In the intestine urobilinogen is formed, some of which is reabsorbed and is again excreted by the liver as urobilin. Nothing is known of the mode of transfer of hemosiderin from the phagocytic cells to the newly growing red corpuscles.

There may be some mechanism regulating the number of corpuscles in circulation. If the concentration of these cells be increased as by an intravenous injection of cells, the excess cells are removed fairly rapidly. This may depend on a temporary cessation of the production of new cells, but the rapidity of the process suggests that cell destruction is also accelerated.

The Spleen

The spleen appears to play a special part in the regulation of the blood volume and of the blood composition, and it is also of primary importance in the destruction of the red corpuscles. It is not, however, essential to life, and the processes of red cell destruction can be carried out adequately in its absence by the rest of the reticulo-endothelial system.

The spleen is supplied by large blood vessels. Its walls and trabeculae are formed of connective tissue and contain a considerable amount of smooth muscle. Large Malpighian follicles of lymphoid tissue, cylindrical in shape, exist within it, as well as a splenic pulp which contains numerous phagocytic macrophages belonging to the reticulo-endothelial system. The arteries entering the spleen eventually connect with venous sinuses which deliver blood to the splenic vein and so to the portal circulation and liver. There appear to be several possible paths between the splenic arteries and the venous sinuses. The

blood may pass through the central arteries of the Malpighian follicles to capillaries which either empty into the follicle or connect directly with the venous sinus. Or it may pass into the splenic pulp; here the vessels may empty into a fenestrated chamber or again pass directly to a venous sinus. The venous sinuses may receive blood directly from the pulp through fenestrations or by tubelike branches that drain directly from the pulp.[26]

The functions of the spleen appear to be storage of reserve red blood corpuscles, destruction of damaged or senile cells by elements of the reticulo-endothelial system, formation of lymphocytes, and defensive immune reactions carried out by the lymphocytes and cells of the reticulo-endothelial system.[11] It is uncertain how the vascular channels are controlled to regulate these processes. It is certain that in dogs the smooth muscle in the walls of the organ can contract and discharge the cells retained within the spleen, whether young or old, to meet emergencies in which extra blood is required, e.g., hemorrhage.[5] It is probable that a similar contraction can occur in man, though the muscle cells of the human spleen are much less developed.

Some of the red corpuscles appear to be modified in the spleen. It is known that the more spherical corpuscles are more readily hemolyzed than those of the normal disc shape. There is evidence that the action of hemolytic sera is associated with the production of a more spherical shape in the cells. It is, therefore, probably significant that cells obtained from the splenic pulp are on the average more spherical than those in the circulating blood. Whether this depends on an action of the spleen which makes the cells more spherical, or whether the spleen is able to select spherocytes for destruction is unknown.[15]

In certain diseases there appears to be overactivity of the phagocytic action of the reticulo-endothelial cells of the spleen. For example, in congenital hemolytic icterus the red cells are more spherical than normal. While removal of the spleen does not lead to the disappearance of the somewhat spherical cells, it does put an end to the excessive cell destruction and consequent anemia. It would appear that the spleen selects and destroys such abnormal cells. In certain diseases the splenic phagocytic cells can show an excessive phagocytosis of leucocytes and thrombocytes. Probably removal of old and damaged members of these groups is also one of the normal functions of the spleen.

Evidence has been advanced that the lymphoid follicles of the spleen can add lymphocytes to the blood.

THE WHITE CELLS OR LEUCOCYTES

The white corpuscles (polymorphonuclear leucocytes of various types, monocytes, and lymphocytes) have functions more related to pathology and immunology than to physiology.[37] The lymphocytes are formed in the lymph glands and in the spleen; all other white cells are formed in the bone marrow. Under resting conditions the total number of these cells is 6,000 per c.mm. of blood (Garrey[13]). With exercise or emotion the numbers may be increased to 10,000 or 12,000. In response to infections the rise may be very much greater. There appears to be no increase following meals except as the result of the activity accompanying the taking of food. The fluctuations in the number of white cells found in the circulating blood probably depend on the side-tracking of

some of these cells in capillaries, where the circulation is sluggish. There the cells may remain as long as the inactivity and sluggish circulation persist.

The polymorphonuclear leucocytes and the monocytes, like the cells of the reticulo-endothelial system, show phagocytic action. They are able to surround and engulf foreign particles and bacteria, and ultimately to digest many such particles. Polymorphonuclear leucocytes that have become engorged with bacteria may themselves be later taken up by the larger phagocytic cells of the reticulo-endothelial system. Phagocytosis is achieved by a process of amoeboid movement. Amoeboid movement also enables the phagocytic cells to approach particles of foreign material. Considerable study has been devoted to the mechanisms involved; apparently some form of chemotaxis is concerned. Thus McCutcheon[28] has examined the movements of human leucocytes on a slide under the microscope. The phagocytic cells make random movements in various directions, but in the presence of a foreign body which exerts an attractive effect, the cells move somewhat erratically toward it. Dried leucocytes and living or dead microorganisms attract phagocytes in this way, but such things as particles of glass or droplets of liquid paraffin exert very slight attraction. No evidence has been obtained of chemotropic effects on lymphocytes. Also lymphocytes do not normally exhibit phagocytosis.[9]

The Thrombocytes

The thrombocytes or blood platelets appear to be derived from the giant cells of the bone marrow, the megakaryocytes. Fragments of the protoplasm of these cells become detached and circulate in the blood as platelets. There they play an important role in blood coagulation (see Chapter XXVIII).

BLOOD PLASMA*

The plasma has a relatively high total osmotic pressure as the result of the electrolytes that it contains, so that it can develop a pressure of 7 atmospheres if separated from distilled water by a membrane permeable to water but totally impermeable to all of its solutes. Such pressures are not developed in the capillaries because their walls are permeable to all the substances contained in the plasma except the large colloid molecules of the proteins. *These, and these only, exert an osmotic force across the walls of the capillaries.* This they do because of the difference in water concentration that they induce, directly by their presence, and indirectly through the uneven salt concentrations that result through the Donnan equilibrium. This osmotic pressure will be discussed later in relation to the conditions in the capillary. The proteins also confer on the plasma a relatively high viscosity, one of the order of 1.8 to 2.1 (compared with distilled water). The viscosity of the whole blood is dependent on the relative amounts of corpuscles and plasma and will be discussed in relation to the circulation (page 408).

In respect to their function of maintaining the colloid osmotic pressure of the blood within the capillaries the plasma proteins may be replaced by other colloids. If an animal be bled in successive stages, the red cells washed with isotonic saline and reinjected suspended in saline, circulation continues only a short while, for the saline is not retained but diffuses into the tissues which

*The important subject of plasma volume and its alterations is discussed in Part VIII.

become edematous. If, on the other hand, the cells are reinjected suspended in a colloidal solution of gum acacia, practically all the serum protein may be removed and yet the animal can recover (Amberson[2]). Within a few days plasma proteins are gradually regenerated and the acacia is slowly removed and stored in the liver.

Though the plasma proteins are not essential for life, at any rate in experiments of short duration, they probably have functions besides that of retaining water and salts within the vascular system. The work of Whipple and his associates[41] indicates that the plasma proteins form one part of a reserve of labile protein that may be used in metabolism. A dog kept on a protein-free diet may be maintained in nitrogenous equilibrium by plasma proteins given intravenously. Globulins of the blood are valuable in immunity reactions. Fibrinogen has an obvious importance in blood coagulation.

Fibrinogen appears to be formed in the liver and there only. Serum albumins are also formed in the liver, possibly also in other parts of the body. Serum globulins may be formed in the liver, but appear to be formed also by reticulo-endothelial cells. Those globulins which act specifically as antibodies in immune reactions also appear to be formed by reticulo-endothelial cells.

The regulation of the formation of plasma proteins is not understood. In health their concentrations in the blood remain fairly constant. One might assume that reversible reactions maintain these concentrations. This, however, cannot be the whole story, for it has been shown that repeated injections of gum acacia (which is a nonprotein colloid) tend to lower plasma protein levels.[43] Therefore it appears that the tendency of the plasma proteins to maintain a more or less steady level in the blood depends more on the fact that they are colloids than on their protein composition. Injection, therefore, either of additional plasma protein or of gum acacia (a glucoside) causes removal of proteins from the blood. Possibly the plasma protein moves into some reserve depot of labile protein, such as is supposed to exist in the liver.

The plasma also supplies to the tissues water and salts in balanced proportions. Many organs including the kidney are concerned in the maintenance of this balance. Under many normal and abnormal conditions rapid transferences of water may occur between the blood and the tissues. The salts usually move with the water. Variations in concentration both of red blood corpuscles and of plasma proteins result from these fluid transfers. Such changes often have clinical importance. They may be measured approximately by determining the specific gravity of whole blood, heparinized (noncoagulable) plasma, or serum, since the density of whole blood is determined largely by the red cells, and that of plasma largely by the protein concentration. The specific gravity may be determined in specific gravity bottles, or by measuring the rate at which drops of blood or plasma fall in solutions of known specific gravity.[4] The latter method has come into clinical use owing to the small amount of blood required. Various estimates of the relation of the specific gravity of the plasma to its protein concentration differ somewhat.[30, 40]

CHAPTER XXVIII

COAGULATION OF THE BLOOD

By Harry Eagle

When blood is removed from the body, it becomes viscous, and soon "sets" to form a semisolid clot of jellylike consistency. The immediate cause of this gelation, or coagulation, is the transformation of one of the plasma proteins, *fibrinogen,* to an insoluble form, *fibrin.* This is deposited as a microscopic network of intermeshing needles which forms the framework of the clot; the cellular elements of the blood, as well as the fluid, are simply caught mechanically in the minute interstices between the compactly bound fibrils.

Subsequent to coagulation, the clot may contract (*syneresis*) and thereby express the clear fluid *serum.* Serum may thus be viewed as plasma from which the fibrinogen has been removed in the form of fibrin. If the blood is whipped or is shaken with glass beads while coagulation is taking place, the fibrin is prevented from forming the usual clot and is deposited as adherent shreds around the glass beads or rod. So-called defibrinated blood is, therefore, a suspension of blood cells in serum. Lymph also clots, as do many inflammatory exudates, and the mechanism is essentially the same as that involved in the coagulation of blood.

The protective value of the coagulation phenomenon in mechanically sealing off wounds and thus preventing an excessive loss of blood is sufficiently obvious. In the rare disease *hemophilia,* characterized by a markedly retarded coagulation, a superficial wound may continue to bleed for hours or days. On the other hand, the same clots which are so essential in preventing the escape of blood from its proper circulatory channels become a menace to health and life when they form within the vascular system. So-called thrombi are local deposits of fibrin and platelets, usually at areas of injury or degeneration along the blood vessel walls. Large numbers of red and white blood cells may be enmeshed in the thrombus, and it may protrude into the lumen of the vessel sufficiently to block the circulation. The resultant anemia or congestion (which of these occurs depends on whether the vessel affected is an artery or vein) may be fatal, as in coronary thrombosis or cerebral thrombosis, or it may cause gangrene of an extremity. A fragment of a thrombus may break off and lodge as an embolus in an end-artery, with immediately serious or even fatal results.

Clearly, the phenomenon of blood coagulation is a nicely balanced defense mechanism which is called into play as soon as blood is shed, but which apparently does not normally occur within the circulating blood. A complete understanding of the process would involve a knowledge of how fibrinogen is converted to fibrin in vitro, why this transformation does not normally occur in vivo, and the reason for the defective coagulation noted in various diseases. These three major aspects of the coagulation phenomenon will be considered in that order.

A. THE MECHANISM OF BLOOD COAGULATION IN VITRO

One of the earliest observations in the study of coagulation was that serum freshly expressed from a clot contains a "fibrin ferment" which will coagulate whole blood, plasma, or purified fibrinogen (Schmidt[171]). Almost all investigators are agreed that the formation of this "fibrin ferment," or, as it is now termed, *thrombin*, is the first phase of the coagulation process. In the second phase, thrombin reacts with fibrinogen to form fibrin.

Several investigators, notably Wooldridge[192, 193] and Nolf,[145-149] have contended that thrombin is a by-product of coagulation rather than its self-evident cause. Others have attempted to explain the entire phenomenon on some simpler basis than that involved in the thrombin theory. Thus, Stuber[175] and his co-workers ascribe coagulation to glycolysis and the release of lactic acid, which presumably then acts on fibrinogen to form fibrin. Hekma[94] considers fibrinogen to be the alkaline hydrosol of fibrin, and views the coagulation phenomenon as a reversible sol-gel formation. The tissue fibrinogen theory of Mills is discussed on page 318. However, in view of the well-established facts, (1) that thrombin may be elaborated from its precursors in the absence of fibrinogen, and thus, in the absence of coagulation (Bordet[20, 21]), (2) that the velocity of coagulation in any mixture varies with the time required for the evolution of thrombin and with the amount produced, and (3) that coagulation is coincident with the sudden liberation of large quantities of thrombin,[47] it seems reasonably certain that thrombin is not an adventitious by-product of coagulation, but its immediate cause.

1. The Formation of Thrombin

Three distinct reagents in shed blood interact to form the coagulant thrombin: (1) ionized calcium; (2) a derivative of blood platelets (or a substance present in tissue extracts); and (3) a plasma factor distinct from either of these, which is called prothrombin.

a. Calcium.—The essential role of calcium was first shown by Arthus and Pagès.[11] If blood is drawn directly into sodium or potassium oxalate, citrate, or fluoride, it remains fluid indefinitely. The oxalate precipitates the blood calcium as the insoluble oxalate, while the citrate and fluoride combine with the calcium to form complex salts with so low a dissociation constant that there is insufficient ionized calcium to cause coagulation. A stock 5 per cent solution of sodium citrate, sodium fluoride, or potassium oxalate will prevent the coagulation of 12, 15, and 50 volumes of blood, respectively. On centrifuging such "decalcified" blood one obtains a fluid plasma which can be manipulated at will, and which can be coagulated by the addition of sufficient calcium salt ($CaCl_2$) to bind the excess anticoagulant and leave a slight excess of calcium ion. As was clearly shown by Hammarsten,[87, 88] and repeatedly confirmed by later workers, the presence of ionized calcium is essential only for the first phase of the coagulation reaction, the formation of thrombin from its precursors in the circulating blood. Once thrombin has been formed, the subsequent removal of calcium by dialysis or by the addition of oxalate has no effect on the coagulating activity.* The presence of ionized calcium is apparently unnecessary for the reaction between thrombin and fibrinogen to form fibrin.

*As yet unexplained is the finding of Ferguson[62] that the activity of freshly elaborated thrombin is markedly diminished by the addition of citrate or oxalate, while similar addition to old thrombin has no effect. Rabinovich[163] has reported that if electrodialyzed thrombin is added to electrodialyzed fibrinogen or plasma, there is no coagulation unless a trace of calcium is also added. The observation should be confirmed, for it clearly has most important implications as to the structure of thrombin.

Calcium can be replaced by salts of either barium or strontium, although neither is as effective as calcium; magnesium salts are practically devoid of activity (Mellanby;[130] Kuwashima[121]).

b. Thromboplastic Factor.*—If decalcified plasma is centrifuged at high speed for a sufficient interval, or if it is passed through a Berkefeld filter, the blood platelets are removed. The platelet-free plasma clots either slowly or not at all on the subsequent addition of calcium in proper concentration,[38] and no thrombin can be demonstrated in the mixture. If, however, platelets are restored to the calcium-plasma mixture, it clots promptly. Bird blood contains relatively stable nucleated "thrombocytes" instead of platelets; if bird blood is collected with care to avoid admixture of tissue fluids (see below), it coagulates very slowly, and may remain fluid for hours. A trace of a mammalian platelet suspension, however, causes its prompt gelation. Clearly, platelets provide a substance which is essential for the formation of thrombin, and thus for coagulation.

Aqueous tissue extracts have the same effect as platelets, and will cause the rapid coagulation of plasma which has been rendered noncoagulable by removal of the platelets. The lung has been found to be particularly rich in the coagulative principle,[136] perhaps because it contains exceptionally large numbers of megakaryocytes and platelets (Howell). Although both red blood cells[169, 192] and leucocytes[148] have been reported to furnish minute quantities of a coagulant resembling that present in platelets or tissue extracts, further confirmation is lacking. It has also been reported that milk accelerates blood coagulation.[119, 173]

Finally, there is now a considerable amount of evidence that plasma as such contains a dissolved substance which acts like platelets and tissue extractives in that it promotes the activation of prothrombin to thrombin by calcium.[86, 124, 126a, 152] The relative importance of the suspended platelets and this dissolved plasma thromboplastin for physiological coagulation is as yet an open question.

The nature of the substance in platelets or tissue which participates in coagulation has been extensively studied.† It is a well-established observation[22, 70, 103, 167, 171, 196] that ethereal or alcoholic tissue extracts have coagulating properties, and can replace platelets or aqueous tissue extracts in initiating thrombin production.

Howell, McLean,[126c] and Gratia and Levene[82] have identified the active substance in these extracts as a phospholipin, cephalin. Charles, Fischer, and Scott[32] have presented evidence that the active substance is not cephalin, but some other lipoid; and Fischer[67] reports that the purer the cephalin preparation, the less active it is in causing coagulation. It must be remembered that such lipoidal extracts are far less active than the original cellular suspension or aqueous extract.[167] Accordingly, it has been suggested (Howell[103]) that the active material in the original tissue is a lipoprotein compound rather than the lipoid as such. It is of interest in this connection that while the coagulative properties of the platelets or crude aqueous tissue extract are destroyed by boiling or by prolonged heating at somewhat lower temperatures, the active substance obtained on the ethereal extraction

*The redundant terminology which makes the study of the coagulation phenomenon so confusing to the student is nowhere better illustrated than here. The terms thrombozyme (Nolf[146, 148]), thrombokinase (Morawitz[140]), zymoplastic substances (Schmidt[171]), cytozyme (Bordet[20, 22]), and thromboplastin (Howell[103]) have all been applied to the platelet or tissue derivative which participates in coagulation; the *tissue fibrinogen* of Mills[136, 137] is probably this same factor.

†A review of the literature on platelets is given by Hittmair.[98]

of these materials is thermostable, and withstands temperatures well over 100° C. It is reported also that the lipoid loses its coagulating activity on the saturation of its double bonds (McLean).

The question as to the nature of the coagulative principle in platelets and tissue extracts further requires reinvestigation in the light of the finding that certain proteolytic enzymes have the same effect in promoting coagulation as the calcium-platelet or calcium-tissue extract mixture (see page 318).

c. Prothrombin.—Even less is known about the third substance involved in the formation of thrombin, namely, prothrombin. Despite reports to the effect that platelets contain not only a prothrombin activator, but prothrombin as well, it is highly improbable that such is the case.[20, 21, 47, 133] A mixture of calcium and platelets does not elaborate thrombin (as it would if platelets contained prothrombin), and the amount of thrombin formed in a calcium-platelet-prothrombin mixture varies directly with the amount of prothrombin used, but is unaffected even by a hundred fold excess of platelets. Prothrombin is largely associated with the globulin fraction of the plasma protein, and this fact is utilized in the preparation of active solutions.

Thus, Howell[104] precipitates the plasma proteins with acetone, and extracts the dried precipitate with sodium bicarbonate. Bordet and Delange[22] find that prothrombin is absorbed by a suspension of tricalcium phosphate, from which it may be recovered by dissolving the precipitate in CO_2 gas. Fuchs[73] has used suspensions of $Mg(OH)_2$ instead of $Ca_3(PO_4)_2$. Mellanby[130] precipitates active prothrombin, along with some fibrinogen and euglobulin, by acidifying water-diluted plasma with acetic acid; the prothrombin is extracted from the precipitate with a solution of calcium bicarbonate. Eagle[47] acidifies the water-diluted plasma with CO_2; the precipitated protein is redissolved, neutralized, and the fibrinogen removed by heating at 56° C. for three to five minutes. Finally, Seegers and his co-workers[172a] have effected a high degree of purification by using a combination of the methods of Mellanby and Fuchs.

The methods used in preparing prothrombin contradict the thesis of Mellanby[127] and of Pickering[153, 154] that blood contains a firmly bound prothrombin-fibrinogen compound stabilized by a hypothetical protective colloid. The two substances may be readily separated by comparatively simple procedures; their association on precipitation with acetic acid or salts is of no more significance than the similar association of fibrinogen and euglobulin, or euglobulin and pseudoglobulin. Repeated precipitations with NaCl or $(NH_4)_2SO_4$ suffice for the preparation of fully reactive fibrinogen containing no demonstrable prothrombin. Moreover, the fact that intravascular coagulation may be caused by the injection of substances which activate prothrombin to thrombin (tissue extracts, trypsin, venoms of *Notechis scutata, Bothrops atrox* or *Bothrops jararaca*) or of agents which act directly on fibrinogen (thrombin, papain, certain *Crotalus* venoms) seems to disprove the theory that circulating blood contains a hypothetical protective colloid which stabilizes a noncoagulable prothrombin-fibrinogen compound. Both the prothrombin and fibrinogen of circulating blood are apparently free and reactive.

The known properties of prothrombin are consistent with the theory that it is a protein. It is destroyed by trypsin or papain in excess,[53] does not dialyze through cellophane, and is precipitated by alcohol and acetone. It has not yet been obtained in pure form; and the nature of the reaction whereby it is converted to an active coagulant, thrombin, is still controversial (cf. next section). Perhaps the most promising approach to the nature of prothrombin and the mechanism of its formation in the body, is that afforded by the work on vitamin K,[22a] summarized in the following paragraphs.

The continued elaboration of prothrombin by the body seems to depend on the adequate absorption of a dietary factor which was termed vitamin K ("Koagulation") by Dam.[2, 3, 39, 40] This dietary factor consists of at least two

substances, vitamins K_1 and K_2,[126b, 176a] the first of which has been identified as 2-methyl-3-phytyl-1,4 naphthoquinone,[65a] and synthesized by two groups of workers.[18a, 64a] Vitamin K_2 has been tentatively identified as 2,3-difarnesyl-1,4-naphthoquinone.[65a] Both K_1 and K_2 have similar physiological activity and may apparently be replaced by other, synthetic naphthoquinones.[5a, 6, 65] In particular, 2-methyl-1,4 naphthoquinone is apparently approximately as active as the naturally occurring vitamin.[6, 177a, 178a] Alfalfa and fish meal are particularly rich in vitamin K, and there is some evidence that substances with vitamin K activity may be synthesized by bacteria in the intestinal contents.[2a, 4, 25]

A normal flow of bile in the intestinal canal is apparently necessary for the proper absorption of vitamin K. When the biliary flow is interfered with, as in experimental bile fistula[83-85, 92, 93] or in human cases of obstructive jaundice or biliary fistula,[25, 41, 168, 171a, 187] the decreased absorption of vitamin K is reflected in a decreased blood prothrombin content. When this falls below 20 per cent of normal, a hemorrhagic tendency develops.[24, 161, 162] In addition, a marked deficiency of prothrombin has been found to occur with some regularity in newborn infants, in whom it averages only 40 per cent of normal, and only gradually reaches or returns to normal levels during the first year of life.[24] There is some difference of opinion as to whether this prothrombin deficiency is present at birth,[24, 95, 182] or develops within a few days.[161a, 161b]

The administration of vitamin K concentrates, of bile, and preferably of both, to experimental animals or human beings with a low blood prothrombin content, usually causes a prompt restoration of prothrombin concentration and coagulability to normal levels.[25, 41, 83-85, 186] Some of the synthetic naphthoquinones have also proved to be therapeutically effective. Exactly how vitamin K stimulates the formation of prothrombin is as yet unknown. There is, however, some evidence that this synthesis occurs in the liver.[168, 185, 186]

d. The Reaction Between Calcium, Thromboplastic Factor and Prothrombin to Form Thrombin.—A mixture of calcium salt, prothrombin, and platelet suspension (or tissue extract) rapidly develops the property of causing the coagulation of fibrinogen or plasma. This is due to the formation of an active coagulant, thrombin. There has been considerable speculation as to the nature of this reaction. The three main theories may be briefly discussed.* (a) The terms thrombozyme, cytozyme, and thrombokinase applied to the platelet or tissue factor by various investigators (see Table X) signify their belief that this factor serves as an activating enzyme which, in the presence of calcium, transforms prothrombin to thrombin. (b) Bordet[20-22] and Mills[133, 134] have been prominently identified with the theory that calcium, platelets or tissue factor (cytozyme), and prothrombin actually *combine* to form thrombin. (c) Howell[102, 103] maintains that prothrombin is activated to thrombin by calcium alone, and that the platelet derivative or tissue extractive, which he terms thromboplastin, serves to remove a hypothetical inhibitor (see page 326). Mellanby,[127] Herzfeld and Klinger, and Pickering[153, 154] also consider thrombin to be a calcium-prothrombin compound.

*Much of the experimental work on coagulation is open to criticism on the score that the reagents used are of unknown activity, and the observations are therefore of qualitative rather than quantitative significance. Stromberg,[124] and Mellanby[88] have utilized a simple method of estimating thrombin activity which is applicable to each of the reagents concerned in the coagulation reaction. Essentially, the method is based on the observation that if all the factors save one are kept constant, the coagulation time will vary with the concentration of this variable.

Mills and his co-workers[136] have postulated two types of blood coagulation. In the one, calcium, platelets, and prothrombin interact to form thrombin, and the thrombin then acts on fibrinogen. In open wounds, however, or whenever blood comes in contact with tissue juices, they believe that a tissue factor which they term *tissue-fibrinogen* combines directly with calcium and blood fibrinogen to form fibrin. Contrary to this theory, however, is the fact that calcium is almost certainly not an intrinsic part of the fibrin molecule (see page 321). Moreover, the crucial experimental evidence for the Mills theory would be the demonstration that the formation of fibrin from tissue extracts, calcium, and fibrinogen occurs in the complete absence of prothrombin; and most investigators,[47, 76, 140-142, 170] have not found this to be the case. Similarly, other workers have shown[8, 140-142, 171] that transudates containing fibrinogen and calcium are not coagulated by tissue juices alone, but require the addition of either prothrombin or thrombin. The data of Mills and his co-workers are probably to be ascribed to the presence of unrecognized traces of prothrombin in their preparations of fibrinogen, tissue extract, or both. In the presence of a large excess of tissue extract this prothrombin would be readily activated to thrombin, which would then cause coagulation. There is certainly no adequate experimental evidence for postulating two wholly unrelated physiological mechanisms for the conversion of fibrinogen to fibrin.

The evidence just cited against the Mills theory is also contrary to the similar theory of Wooldridge.[192, 193]

The available data concerning the kinetics of thrombin formation and the reacting proportions of calcium, thromboplastin, and prothrombin, offer no apparent clue to the nature of the reaction. Extraordinarily minute amounts of thromboplastin (cephalin, platelets, or tissue extractives) suffice to transform prothrombin to thrombin quantitatively. Even a hundred fold increase in excess of this minimum quantity continues to increase the velocity of thrombin formation;[47]* while below the minimal effective concentration, the amount of thrombin formed varies directly with the amount of thromboplastin used.[62a, 172b] Although calcium may be precipitated quantitatively from formed thrombin without affecting its coagulating activity,[48, 87, 88] and although minimal amounts of cephalin or thromboplastin suffice for thrombin formation, these findings do not exclude the possibility that either thromboplastin or calcium, or both, are intrinsic parts of the thrombin molecule. The molar concentration of thrombin in the most active preparations yet available is extraordinarily minute, probably less than 10^{-6} molar; and the amount of calcium or tissue extractive represented by this concentration would escape detection by ordinary analytical procedures.

The data just cited are consistent with any of the three theories of the mechanism of thrombin formation. There are, however, some additional findings which suggest that Morawitz and the others, who, almost intuitively, considered the thromboplastic factor to be an enzyme which acts on prothrombin to form thrombin, may have been correct in that surmise. Mellanby[131] has observed a spontaneous activation of prothrombin to thrombin, and Cekada[27] has reported its activation by a wide variety of chemical agents. These observations are as yet unconfirmed, but suggest that thrombin may not be a calcium-platelet-prothrombin compound. Perhaps the most significant evidence for the enzyme thesis is the fact that both crystalline trypsin, and certain proteolytic snake venoms (notably the venoms of *Notechis scutata, Bothrops atrox*, and *Bothrops jararaca*) which are active in extraordinarily high dilutions, directly activate

*This finding justifies the use of the term *prothrombin* for this factor, in preference to the term *serozyme* used by Bordet.[20] The term *thrombogen* (Morawitz)[142] also conforms to the experimental findings, and would be equally satisfactory. In the interest of uniformity, however, it should be discarded in favor of the generally accepted term *prothrombin*. *Prothrombase* (Mellanby[130]) and *plasmozyme* (Fuld and Spiro[76]) imply an enzyme function for thrombin which, however probable, is still debatable.

prothrombin to thrombin in the absence of either ionized calcium or free thromboplastin.[51, 53] Unless one assumes[63, 132b] that these enzymes liberate calcium and active thromboplastin from an inert combination with protein, this strongly suggests that the conversion of prothrombin to thrombin is activated by proteolytic enzymes.

A striking analogy for the enzyme theory of prothrombin activation is furnished by the reaction between enterokinase and trypsinogen to form trypsin, or that between chymotrypsinogen and trypsin to form chymotrypsin (Kunitz and Northrop). It is an open question whether the hypothetical calcium-thromboplastic enzyme (or trypsin or snake venom) merely initiates a molecular rearrangement of prothrombin, actually hydrolyzes prothrombin, or perhaps combines with it to form thrombin. If the latter is the case, both Morawitz and Bordet were correct, the former in considering the platelet factor to be an enzyme, the latter in postulating chemical combination between the platelet factor and prothrombin.

It may be said in summary that a plausible working hypothesis as to the nature of the reaction between calcium, thromboplastin, and prothrombin is that calcium and thromboplastin together constitute an enzyme system which, like trypsin and certain proteolytic snake venoms, activates prothrombin to thrombin. As will be shown in the following section, there is reason to believe that the product of this reaction, thrombin, is itself a proteolytic enzyme (see Tables VIII and IX). The matter cannot, however, be regarded as closed. An obvious weakness in this enzyme theory is the fact that lipoidal tissue extracts, acting in conjunction with calcium, also convert prothrombin to thrombin.

TABLE VIII

A TENTATIVE WORKING HYPOTHESIS AS TO THE NATURE OF THE REACTION BETWEEN CALCIUM, PLATELETS, AND PROTHROMBIN TO FORM THROMBIN (After Eagle and Harris[53])

Calcium and platelets (or calcium and tissue extracts) together constitute a proteolytic enzyme which, like trypsin and snake venoms, reacts with its substrate, prothrombin, to form thrombin. The resultant thrombin is itself a proteolytic enzyme (see Table IX, page 322):

SUBSTRATE		ACTIVATING ENZYME		ENZYME PRODUCT
Prothrombin	+	Ca-platelets Ca-tissue extract Plasma thromboplastin? Trypsin Venoms of *Bothrops atrox, Bothrops jararaca, Notechis scutata,* and several other proteolytic venoms Bacterial proteases?	→	Thrombin

An analogy for this hypothesis is to be seen in the similar enzymic activation of chymotrypsinogen or trypsinogen:

Chymotrypsinogen	+	Trypsin	→	Chymotrypsin
Trypsinogen	+	Enterokinase	→	Trypsin

2. The Reaction Between Thrombin and Fibrinogen to Form Fibrin

a. Thrombin.—To obtain a solution of thrombin, one need only add calcium and a trace of tissue extract to the solution of prothrombin. Alternatively, a fresh clot may be washed free of cells, squeezed, minced, and extracted with 8 per cent salt solution for forty-eight hours in the ice box (Gamgee; Howell[101]). Preliminary extraction of the clot with ether facilitates the subsequent extraction

of thrombin (Roberts[165]). The direct activation of solutions of prothrombin is a simpler procedure, and yields more uniform and more active solutions.

Thrombin preparations consist largely of protein, and it is possible that even in the purest preparations yet obtained, the active thrombin constitutes only a small proportion of the total solids. The thrombin itself is apparently a protein, although there is some evidence that it may be of smaller molecular size than prothrombin. Thus, Mellanby[131] reports that thrombin, unlike prothrombin, slowly diffuses through a cellophane membrane.

Thrombin is destroyed by such proteolytic enzymes as trypsin or papain, and is partially inactivated by heating at temperatures exceeding 70° C. It is reported, however, that solutions may retain some activity even after boiling, and that in the dry state thrombin may be heated to 135° C. without inactivation (Wöhlisch,[190] page 509). On the other hand, Mellanby[130] finds that thrombin is inactivated in three minutes at 55° C. Solutions of thrombin kept at 0° to 5° C. may remain active for weeks, particularly if the solution is made strongly hypertonic; and thrombin kept in the frozen state may be active after months. Thrombin, as well as its precursor, prothrombin, is rapidly and completely inactivated on coupling with diazo compounds.

b. Fibrinogen.—This protein, with which thrombin reacts to form fibrin, is one of the most labile of the plasma proteins. Estimates as to the amount normally present in human plasma range between 0.2 and 0.5 per cent. It is completely coagulated on heating at 56° C. for five to ten minutes, and is more susceptible to precipitation by neutral salts than either euglobulin, pseudoglobulin, or albumin. Thus, it is precipitated from solutions by half-saturation with sodium chloride, by 25 to 30 per cent saturation with ammonium sulfate, or (at 37° C.) by 0.75 molar sodium sulfate.

The simplest method of preparing relatively pure fibrinogen is to free citrated or oxalated blood of all cellular material by prolonged centrifugation, and to precipitate the fibrinogen from the clear plasma by adding slightly more than an equal volume of saturated sodium chloride at room temperature. When the mixture is centrifuged, the precipitated protein is collected as a compact, glutinous layer. This is now redissolved in a minimum volume of water and reprecipitated by adding saturated sodium chloride in a volume slightly greater than the amount of water used to redissolve the fibrinogen. It is advisable to add a trace of citrate to the salt solution in order to avoid the activation of prothrombin by traces of calcium present in the sodium chloride. A total of three precipitations usually suffices to yield a solution of fibrinogen which fails to coagulate on the addition of calcium and tissue extract. The more care used in expressing the free fluid from the precipitated fibrinogen, the fewer precipitations are necessary.

Fibrinogen keeps much better in hypertonic solution than it does in 0.85 per cent sodium chloride, and solutions stored at 0° to 5° C. may remain serviceable for one to two weeks. If kept in the frozen state in a tightly-stoppered container, hypertonic fibrinogen solutions remain active for many weeks. The solutions exhibit the property of double refraction of flow (Wöhlisch and Clamann[191]), indicating that the molecules of dissolved fibrinogen assume a definite orientation in a streaming fluid. This tendency to orient may be related to their "crystallization" as long needles during the process of coagulation. One frequently observes spontaneous gelation of solutions of fibrinogen, and the relation of this slow coagulation to that which occurs physiologically is an open question.

The protein is readily denatured by shaking, probably because it forms an adsorbed film at the air-water interface. This denaturation of the surface film can be readily demonstrated by rapidly expelling a concentrated solution of fibrinogen through a pipette against the side of a glass tube. The surface of the fluid immediately adjacent to the point of impact is covered with a crinkled insoluble film of protein.

The most diverse figures are given in the literature for the isoelectric point of fibrinogen.[190] They range from pH 4.4 to 8.0, but most of the data center around 4.5 to 6.0. Thus, as regards isoelectric point, fibrinogen does not significantly differ from the other plasma proteins.

The origin of fibrinogen has been extensively studied by Doyon, Nolf, Whipple and their co-workers, all of whom concluded on the basis of experiments involving hepatic injury, extirpation, or circulatory blockade, that the liver is primarily concerned in its formation (see Wöhlisch,[190] p. 538). No regeneration of fibrinogen can be demonstrated in hepatectomized rabbits (Drury and McMaster[44]). The participation of bone marrow has been suggested by Müller and by Morawitz and Rehn.[143]

The experimental data cited on page 316 seem to invalidate the theory[60, 127, 153, 154] that fibrinogen is present in the circulating blood as a stable, noncoagulable prothrombin-fibrinogen complex.

c. The Reaction Between Solutions of Thrombin and Fibrinogen.—The reaction between these solutions is striking. With a sufficient excess of thrombin, only a few seconds may be required for the opalescent fluid mixture to become an opaque white rigid gel. If less thrombin is used, coagulation is correspondingly delayed, and visible fibrils appear only after a latent period which may be as long as twenty-four hours. If the reaction is viewed under the dark-field microscope, one sees that the apparently homogeneous gel is actually made up of myriads of fine intermeshing needles (fibrin) which have "crystallized" from solution and entrapped the fluid. The size of these needles varies according to the concentration and age of the fibrinogen and thrombin, the speed of coagulation, and the pH of the solution; indeed, in sufficiently alkaline reaction, no needles can be demonstrated, and the slowly formed, soft clot is translucent and opalescent instead of opaque and white (see Howell;[102] Barratt[12]). Despite its apparent rigidity, the fibrin clot consists of over 99 per cent water and less than 1 per cent solid, as contrasted with the approximately 50-50 ratio in the case of coagulated whole blood. The solid residue, freed as completely as possible from the enmeshed fluid, is fibrin.

No clear-cut chemical difference between fibrinogen and fibrin has yet been discovered. Their tryosine, tryptophan, and cysteine contents are identical. Anson and Mirsky[7] have found that, in contradistinction to heat-denatured proteins, fibrin does not contain an increased number of SH or SS groups. Although Mellanby[127, 131] believed that fibrinogen is split by thrombin into fibrin and a soluble globulin, there is no satisfactory evidence that such is the case. With carefully purified fibrinogen, more than 95 per cent is recovered as fibrin; it is entirely probable that the remainder is not globulin split from the fibrinogen (as indeed, it could not be unless one assumed approximately a 20:1 disparity in molecular weights), but plasma euglobulin incompletely removed during the preparation of the fibrinogen. Contrary to previous reports, there is no demonstrable change in hydrogen ion concentration during the coagulation of whole blood, plasma, or fibrinogen solutions.[52, 64] The data on changes in conductivity or heat of reaction are conflicting, and require reinvestigation. Finally, it seems clear that calcium cannot be an intrinsic part of the fibrin molecule unless one makes some unjustifiable assumptions. Strongly oxalated solutions of thrombin will coagulate similarly oxalated solutions of fibrinogen prepared from citrated or oxalated plasma and containing 0.5 per cent protein. The solubility product of calcium oxalate being approximately 2×10^{-9} at room temperature, in a solution containing 0.02 M oxalate, this implies a maximum concentration of approximately 10^{-7} molar ionized calcium. Even if we assume that all this calcium is incorporated in the fibrin, it follows that calcium cannot be considered an intrinsic part of fibrin unless one assumes either that fibrin has a molecular weight of the order of ten to fifty million, or that calcium is an intrinsic part of fibrinogen, present as a nonionized complex salt not precipitable by oxalate, for which there is no experimental evidence.

In the absence of any demonstrable chemical difference between fibrinogen and fibrin, there has been considerable speculation as to the mechanism whereby thrombin effects the transformation.

The correlation between coagulation time, thrombin concentration, and fibrinogen concentration does not conform to any simple chemical reaction, and offers no clue as to the nature of the coagulation phenomenon.[48, 69, 181] Attempts to establish the quantitative relationships between thrombin, fibrinogen, and fibrin are invalidated because of the slowness with which equilibrium is reached, the deterioration of both thrombin and fibrinogen during that time, and the adsorption of thrombin by the clot.[48, 68, 78, 129] There are some who believe that thrombin combines with fibrinogen to form an insoluble compound, fibrin. Most of the accumulated experimental data, however, indicate that thrombin is a proteolytic enzyme ("fibrin ferment" of Schmidt) which reacts with a specific substrate, fibrinogen, to form fibrin as a product of hydrolysis.

A highly active thrombin preparation may coagulate as much as 10,000 times its weight of fibrinogen. In view of the fact that so-called thrombin solutions contain a large amount of inert protein, the true ratio is probably even higher. Such a disproportion is difficult to reconcile with any theory of chemical combination, and strongly suggests an enzyme reaction. It is true that some of the thrombin disappears during its reaction with fibrinogen, but this is consistent with the enzyme theory. The thrombin does not begin to disappear as soon as it is added to fibrinogen, as one would expect if combination were taking place, but only after a long latent period, and coincident with the beginning of coagulation. Moreover, the amount which disappears may be several hundred times greater than the minimum quantity necessary to induce coagulation, strong evidence that the thrombin is merely adsorbed by the fibrils of the fibrin clot.[48, 127] The fact that thrombin may be readily extracted from the clot further supports the thesis that it is not an intrinsic part of the fibrin. Solutions of presumably "pure" fibrinogen frequently gel spontaneously after several days at refrigerator temperatures, to form clots indistinguishable from fibrin. One can only speculate as to whether this coagulation is due to the formation of thrombin from traces of residual prothrombin or whether it is truly a spontaneous conversion of fibrinogen to fibrin. In the latter event, thrombin would simply be an enzyme which enormously accelerates a reaction which occurs, however slowly, in its absence.

Strong additional evidence for the thesis that thrombin is a proteolytic enzyme is furnished by the observation that other proteolytic enzymes also act on fibrinogen to form fibrillar gels indistinguishable from fibrin. One of these is papain, the enzyme present in the juice of the papaw.[53] A large number of proteolytic snake venoms are likewise effective.[10, 50, 100, 125] These venoms are known to contain active proteolytic enzymes and the effectiveness of high dilutions suggests that their activity is due to their enzymic action.[50] It may be noted that at least three venoms not only act on fibrinogen directly, but also act on prothrombin to form thrombin (see page 318). There is some evidence also that the coagulating action of certain bacteria, notably staphylococci, on citrated blood or plasma is in part a direct one on the fibrinogen.[81, 184] Finally, the observation[132c] that solutions of prothrombin are inactivated by thrombin is consistent with the thesis that thrombin is a proteolytic enzyme.

In summary, the available evidence strongly suggests that thrombin is a proteolytic enzyme which converts fibrinogen to an insoluble modification, fibrin, although it is an open question whether actual proteolysis is involved. Taken in

TABLE IX

A TENTATIVE WORKING HYPOTHESIS AS TO THE NATURE OF THE REACTION BETWEEN THROMBIN AND FIBRINOGEN TO FORM FIBRIN (AFTER EAGLE[50])

Thrombin is a proteolytic enzyme which, like papain and certain snake venoms, hydrolyzes fibrinogen to form fibrin.

PROTEIN SUBSTRATE		PROTEOLYTIC ENZYME		PRODUCT
Fibrinogen	+	Thrombin Snake venoms Papain Bacterial proteases?	→	Fibrin

conjunction with the data indicating that *calcium plus thromboplastin* may also constitute an enzyme system, one may therefore formulate the working hypothesis that a calcium-thromboplastin enzyme activates prothrombin to form a new enzyme, thrombin. This theory is diagrammatically summarized in Table IX. The analogy of this to the activation of chymotrypsinogen by trypsin to form chymotrypsin is to be particularly noted (see Table VIII, page 319).

3. Syneresis and Fibrinolysis

When blood clots spontaneously, or when decalcified blood or plasma is coagulated by the addition of calcium, the clot usually contracts over a period of hours (syneresis), and as it does, fluid serum is expressed, much as water would be squeezed from a sponge. On the other hand, if the platelets are removed from decalcified plasma by Berkefeld filtration, and if coagulation is then induced by the addition of calcium and platelet (or tissue) *extracts,* the clot does not contract spontaneously, and the serum must be expressed mechanically. Bird blood, which contains no platelets, does not retract. Again, no syneresis is observed if the decalcified blood is coagulated by preformed thrombin, by snake venoms which act as thrombin,[50] or by those agents which convert prothrombin to thrombin without the necessary intervention of platelets (trypsin, *Bothrops atrox and Bothrops jararaca* venoms[53]). Clearly, as was first shown by Fonio, syneresis is obtained only when platelets actively participate in the formation of thrombin, and even then only if fibrinogen is present while the thrombin is being elaborated. The more platelets present during coagulation, the faster and more complete is the subsequent retraction of the clot. If the platelets are reduced below a critical level, estimated by Opitz and Schober[150] to be 45,000 per c.mm., there may be no retraction despite the presence of sufficient platelets to initiate thrombin production and coagulation. This is the state of affairs in the pathological condition, purpura hemorrhagica (cf. page 329).

The mechanism whereby platelets initiate clot retraction is still obscure. It has been suggested[74] that coagulation proceeds more rapidly in the immediate vicinity of each platelet, the resultant irregularities in the distribution and size of the fibrin needles within the clot setting up stresses which result in retraction. It has also been suggested[122] that, because of a local accumulation of platelets in contact with a foreign surface, coagulation begins in the periphery and thence extends into the center of the blood mass. Lampert[122] believes that syneresis results from this uneven rate of coagulation, supplemented by the serum-attracting tendency of the walls of the container. Tocantins[179] has presented evidence that platelets accumulate at fibril intersections, and by agglomeration and fusion cause a twisting and bending of the fibers. Finally, Hirose[97] believes that the retraction of the clot is due to digestion of the fibrin. Further work as to the mechanism of clot retraction is clearly indicated.

Apparently distinct from clot retraction is the spontaneous re-solution of the fibrin which is occasionally observed, a phenomenon known as *fibrinolysis.* The originally rigid clot gradually softens and, in the absence of bacterial contamination, goes completely into solution after a period of hours or days. The mechanism of this process is as yet unknown. It is to be noted in this connection that certain strains of streptococci isolated from cases of human infection elaborate a substance (fibrinolysin) which causes a remarkably rapid lysis of fibrin clots (Tillett and Garner[178]). Interestingly enough, this lysin usually attacks only fibrin clots in which either the fibrinogen, thrombin, or both, are of human origin. Rabbit fibrinogen coagulated by rabbit thrombin is usually unaffected

by the lysin. Whether the slow spontaneous lysis of blood clots is to be attributed to a similar fibrinolysin, distinct from thrombin, and perhaps derived from the leucocytes, or whether it is caused by thrombin per se (see Cekada[27a]), is a subject for future study.

4. Summary

The phenomenon of blood coagulation depends on the transformation of one of the plasma proteins, fibrinogen, to an insoluble fibrous gel, fibrin. This transformation involves two consecutive reactions. In the first of these, calcium, a thromboplastic factor present in blood platelets and perhaps in plasma as well, and a plasma factor termed prothrombin react to form an active coagulant, thrombin. Thrombin then reacts with fibrinogen to form fibrin. Although the available evidence does not justify any definite conclusion as to the nature of these reactions, it does strongly suggest that calcium and the thromboplastic factor together may constitute a proteolytic enzyme which acts on the prothrombin. It is probable that the product of this reaction, thrombin, is itself a proteolytic enzyme which transforms fibrinogen to fibrin.

B. THE NATURE OF THE PHYSIOLOGICAL ANTICOAGULANT

Perhaps the most puzzling aspect of the phenomenon of blood coagulation is the fact that in the intact animal the fibrinogen of the circulating blood remains unchanged, despite the presence of those elements which convert it to fibrin in the test tube (calcium, platelets, prothrombin). Such intravascular coagulation would obviously be incompatible with life. The nature of the body's highly effective protective mechanism is still an elusive riddle. Many theories have been propounded, and the numerous pro- and anti- factors which render the literature on coagulation so confusing represent ingenious but conflicting attempts to solve the problem (Table X). As will appear, however, there is reason to doubt that any one of these theories is an adequate explanation of the known facts.

1. Antithrombin* (Peptone Plasma, Anaphylaxis Plasma)

Circulating blood, or blood prevented from coagulating by the addition of a suitable anticoagulant, has the property of inactivating thrombin. In consequence, serum expressed from a fresh clot gradually loses its ability to coagulate fibrinogen. For the same reason, considerably more thrombin is required to coagulate plasma than is required to coagulate an equivalent quantity of purified fibrinogen. The substance in whole blood, plasma, or serum which inactivates thrombin has been termed *antithrombin,* and the thrombin-antithrombin "compound" has been termed *metathrombin.* The inactive serum containing this compound may be reactivated† merely by the temporary addition of an equal

*The term *antithrombin* has been applied indiscriminately by various workers to many factors which inhibit coagulation, regardless of whether these factors affect prothrombin, platelets, or formed thrombin. The subject is sufficiently complicated without the added confusion of a loose terminology. Accordingly, *antithrombin* is here used in its strict sense, as a substance which neutralizes formed thrombin. It may be that some antithrombins also inhibit the formation of thrombin from its precursors; but even if true, this only accentuates the necessity for precise definitions.

†This reappearance of thrombin on the temporary alkalinization of an apparently inactive serum is to be distinguished from the formation of new thrombin often observed on adding platelets or tissue extracts to serum. In the normal course of coagulation, not all of the prothrombin is converted to thrombin, perhaps because the platelets become enmeshed in the clot and are thereby prevented from carrying the reaction to completion. The residual prothrombin in the serum is, however, promptly converted to thrombin on the addition of an activating platelet suspension or tissue extractive.

TABLE X

SOME OF THE THEORIES AS TO THE MECHANISM OF COAGULATION (AFTER EAGLE[47, 51])

	AUTHOR*	ACTIVE PARTICIPANTS IN THE PROCESS IN ADDITION TO FIBRINOGEN AND CALCIUM†		INHIBITORY FACTORS	SUPPOSED SEQUENCE OF EVENTS
		PLASMA FACTOR	PLATELET OR TISSUE FACTOR		
Thrombin Theories of Coagulation	Schmidt[171]	Prothrombin	Thromboplastin Zymoplastic substance	"Cytoglobin," an antithrombin	Prothrombin + zymoplastic substance → thrombin Thrombin + "fibrinoplastic substance" + fibrinogen → fibrin
	Hammarsten[87, 88]				— — — → thrombin Thrombin + fibrinogen → fibrin
	Morawitz[140-142]	Thrombogen	Thrombokinase	Antithrombin	Thrombokinase + thrombogen + Ca → thrombin
	Fuld and Spiro[56]	Plasmozyme	Cytozyme		Thrombin + fibrinogen → fibrin
	Mellanby[127, 128] Pickering[153, 154]	Prothrombin		An unidentified inhibitory factor stabilizing a prothrombin	Stabilizing factor is somehow destroyed in vitro, allowing calcium to activate prothrombin-fibrinogen complex to form fibrin
	Bordet[20-22]	Proserozyme	Cytozyme	A plasma inhibitor affecting serozyme	Proserozyme —(calcium, contact)→ serozyme Serozyme + calcium → thrombin Thrombin + fibrinogen → fibrin
	Howell[101-111] Fuchs[75]	Prothrombin	Thromboplastin Cephalin	Antithrombin Antiprothrombin (heparin) Pro-antithrombin	Prothrombin — antiprothrombin + cephalin → prothrombin + cephalin — antiprothrombin Prothrombin + calcium → thrombin Thrombin + fibrinogen → fibrin
Nonthrombin Theories	Wooldridge[193]	Fibrinogen B	Tissue fibrinogen (Fibrinogen A)		Blood fibrinogen A + tissue fibrinogen B → fibrin + thrombin
	Nolf[145-148]	Thrombogen	Thrombozyme		Thrombozyme + thrombogen + calcium + fibrinogen → fibrin + thrombin
	Mills[133-136]	Blood fibrinogen	Tissue fibrinogen		Blood fibrinogen + tissue fibrinogen + calcium → fibrin
	Stuber[175]	Glucose			Glucose → lactic acid Acid + fibrinogen → fibrin
	Hekma[94]				a. Fibrinogen —(acid, base)→ fibrin b. Fibrin = fibrinogen "agglutinated" by thrombin

*For general reviews, see Fonio,[69] Howell,[106, 108] Morawitz,[142] Nolf,[140] Pickering,[154] Wöhlisch,[190] Fuchs,[75] Zunz.[197]

†The essential role of calcium in coagulation was first recognized by Arthus and Pagès.

volume of tenth normal sodium hydroxide and subsequent neutralization.[164, 171, 177] Despite a large literature, the chemical nature of antithrombin, the mechanism whereby the thrombin is inactivated, and the reason for its reactivation on the addition of alkali, are wholly obscure.

The possible value of antithrombin in counteracting any slow liberation of small quantities of thrombin which might occur in vivo requires no discussion. It is, however, equally apparent that the antithrombic action of blood is not sufficiently pronounced to counteract the rapid formation of large amounts of thrombin which occurs in shed blood. Contrary to earlier reports,[101, 153, 192] the intravenous injection of thrombin causes prompt intravascular coagulation and death.[51, 131] Furthermore, the amounts necessary are approximately the same as would be necessary to coagulate that same amount of blood in vitro.

It is clear that circulating blood fails to clot primarily because there is some protective mechanism which minimizes thrombin formation in vivo to such an extent that the antithrombin normally present is an adequate safeguard.

It is true that under certain conditions there is an extraordinary increase in the amount of antithrombin, sufficient to prevent coagulation even in vitro. If Witte's peptone is injected intravenously into dogs (approximately 0.3 Gm. per kg.) the animal is profoundly shocked; the shed blood either coagulates very slowly, or remains fluid indefinitely. Similarly, if rabbits or dogs are sensitized to a foreign protein, and are then given a severe anaphylactic shock by the intravenous injection of that protein, their blood often becomes noncoagulable. In both cases, the failure of the blood to coagulate is due to an enormous increase in its antithrombic activity.[54, 149, 159, 189, 198] More recent work[159, 188, 189] has shown that in both cases the antithrombic factor is actually heparin, probably arising from the liver.[188]

It is an open question whether the relatively weak antithrombic activity of normal plasma is due to the presence of correspondingly small amounts of heparin (vide infra) or to some wholly unrelated factor. It is, however, clear that under physiological conditions, the antithrombic action of circulating blood or plasma is not sufficiently pronounced to prevent coagulation. Some other factor must contribute to the stability of circulating blood.

2. Pro-prothrombin

Bordet[20, 21] suggested that circulating blood contains, not prothrombin (serozyme) as such, but an inactive precursor of prothrombin which he termed *proserozyme.* On contact with some foreign surface, such as glass, the proserozyme is somehow converted to serozyme, which then reacts with calcium and platelet factor to form thrombin. The experimental evidence for the presence of a pro-prothrombin in circulating blood is meager. Moreover, the fact that tissue extracts, trypsin, or the venoms of *Notechis scutata, Bothrops atrox* or *Bothrops jararaca* injected intravenously immediately convert prothrombin to thrombin, and thus cause intravascular coagulation and death, indicates that prothrombin is present as such in circulating blood.

3. Prothrombin-Fibrinogen Complex

The theory of Mellanby,[127] Pickering[153, 154] and Feissly[60] that circulating blood contains an inactive prothrombin-fibrinogen complex stabilized by an unidentified protective colloid has been discussed on page 316.

4. Heparin, Antiprothrombin and Pro-antithrombin

In 1918, Howell and Holt[111] extracted a powerful anticoagulant from liver which they termed *heparin,* and considered to be the physiological substance

which prevents blood from coagulating in vivo. This has since been obtained from many other tissues, particularly the brain and lung,[65b, 73, 107, 189] and has been isolated in crystalline form as a Ba-salt by Charles and Scott.[34] The mast cells are said to be particularly rich in heparin, and to be perhaps the primary physiological source of the material.[99, 114, 118] Jorpes and his co-workers[113, 116, 117] have identified heparin as a mixture of polysulfuric esters of mucoitin, containing acetylated glucosamine as the hexosamine, and probably glucuronic acid as the hexuronic acid. However, the crystalline heparin of Charles and Scott seems to be homo-molecular. Other polysulfuric acids, both natural and synthetic,[14, 15, 28, 30] have been found to have a qualitatively similar, if less pronounced, anticoagulant action. Protamine[29, 31] and benzidine[16] combine with and neutralize the activity of heparin, presumably because their basic groups combine with the sulfuric acid radicals of the anticoagulant.

A prolonged controversy as to the mechanism whereby heparin exerts its anticoagulant action seems to have established that, as originally stated by Howell, it both inhibits the transformation of prothrombin to thrombin,[23, 37, 62b] and neutralizes formed thrombin.[132, 158, 172, 185] Again confirming Howell, the weight of evidence now indicates that the antithrombic activity of heparin is not apparent in the absence of serum or plasma. Moreover, it has been reported[23] that its inhibitory effect on the formation of thrombin also requires the presence of some plasma factor. The nature of the plasma constituents with which heparin reacts to form these two inhibitors is as yet unknown; and it is possible that the same plasma component may be involved in both instances. The mechanism whereby a heparin-plasma complex inhibits thrombin formation is still speculative. The active anticoagulant may combine with and thus neutralize either thromboplastin or prothrombin, or it may exert its inhibitory action through some wholly unrelated process.

Purified heparin preparations are remarkably powerful anticoagulants; thus, as little as 1 mg. may prevent the clotting of 100 ml. of blood for twenty-four hours. Moreover, not only has heparin been isolated from many body tissues, but under certain conditions, it may apparently be released into the blood from the liver[159, 188, 189] in sufficient concentration to render the blood noncoagulable (peptone shock, anaphylactic shock). It is nevertheless still debatable whether heparin is normally present in the blood, and if so, whether it is the physiological anticoagulant which keeps blood fluid in vivo. Although its isolation from normal blood has been reported,[65b, 73, 107] Jorpes[114, 115] has pointed out that it cannot be demonstrated in circulating plasma by a color test (toluidine blue) sensitive to 1.5-3.0 gamma per cent. Moreover, Quick[159] has pointed out certain qualitative differences between the antithrombin of normal blood and that present in heparinized blood. Finally, the very fact that shed blood does clot indicates that heparin cannot be the only factor involved in the maintained fluidity of the circulating blood.

5. Platelet Stability or an Inactive Plasma Thromboplastin as the Physiological Defense Mechanism Against Intravascular Coagulation

Indeed, if one is willing to accept the thesis that the platelets in circulating blood are stable, and only disintegrate to release an active thromboplastin when blood is removed from the body, it becomes unnecessary to invoke any hypothetical antifactor as the physiological anticoagulant. On the basis of

this theory, calcium and the platelet factor together transform prothrombin to thrombin in vitro, perhaps because they constitute a proteolytic enzyme analogous to trypsin, and this transformation may fail to occur in vivo solely because the platelets remain intact and inactive. This concept of platelet stability in vivo as the body's chief defense mechanism against intravascular coagulation has the virtue of simplicity. As an explanation this faces less contradictory evidence than any of the theories previously cited. Nevertheless, it is not wholly satisfactory.

In the first place, there is no conclusive evidence as to the nature of the change effected in platelets in shed blood. It is true that platelets have been observed to disintegrate soon after blood is removed from the body and immediately before coagulation begins.[61, 176, 194] Indeed, if blood is kept from coagulating by the addition of heparin, citrate, or some other anticoagulant, the platelets do not agglutinate and disintegrate, but remain remarkably stable. There is, nevertheless, some indication that complete disintegration may not be an essential preliminary to coagulation. If platelets are removed from citrated plasma by centrifugation, the platelet suspension retains its coagulating activity despite repeated washing, even in the presence of calcium salts; moreover, a large part of the coagulating activity is usually recovered in the washed sediment. Clearly, fragments of platelets sufficiently large to be easily sedimented, are nevertheless capable of initiating coagulation. If something does happen to platelets in shed blood which makes them capable of changing prothrombin to thrombin, it may be some change more subtle than complete disintegration.

The second weakness in the theory of platelet-stability as the body's bulwark against intravascular coagulation is the fact that, regardless of whether the platelets disintegrate or undergo some more obscure "activation," the factor presumably responsible has not as yet been satisfactorily identified. Although it has been generally accepted that calcium and plasma promote the disintegration or "activation" of platelets,[37, 38, 194] this is clearly not the body's defense against intravascular coagulation, for ionic calcium is present in the circulating plasma. It has been suggested that contact with a foreign surface, such as glass, sets into action a trigger mechanism which activates platelets and thus initiates the formation of thrombin.[79, 80] In support of this contention is the fact that blood collected under oil, in a paraffined container, with due precautions to avoid the admixture of tissue juices, remains fluid far longer than blood collected in a glass container. Lampert[122] has presented evidence that the velocity of coagulation varies directly with the degree to which platelets are adsorbed on the walls of the container. In containers made of amber or artificial resins, in which this surface accumulation of platelets does not occur, he has observed a remarkable prolongation of both coagulation and of syneresis.

Similar to the theory of platelet degeneration is the thesis that plasma contains a dissolved material which is somehow activated by contact with a foreign surface to form an active thromboplastin.[17, 79, 122] The recent demonstration of a factor in normal cell-free plasma which promotes the transformation of prothrombin to thrombin[126a, 151, 152, 156] is suggestive in this connection. The clear-cut proof that plasma does contain a dissolved thromboplastin which is activated only after contact with a foreign surface would resolve some of the most puzzling aspects of the coagulation phenomenon.

6. Summary

It is abundantly clear that the problem as to why circulating blood fails to clot cannot be regarded as solved. The most plausible explanation yet suggested is that the thromboplastin of the circulating blood is present in an inactive form, and that it becomes available in shed blood through either the disintegration of blood platelets or the activation of a dissolved plasma factor by contact with a foreign surface. It is an open question whether, as a second line of defense, heparin may not be present in the circulating blood in sufficient concentration to counteract the effect of such small amounts of active thromboplastin as may be liberated in vivo. The possibility must, however, be considered that the body's true defense against intravascular coagulation may be some substance or factor not envisaged in any of the theories previously discussed.

C. CLINICAL ASPECTS OF THE COAGULATION PHENOMENON

1. Coagulation Time

The determination of the time required for blood to coagulate after it is withdrawn from the body is a widely used diagnostic procedure. If the results obtained from day to day, or from patient to patient, are to be comparable, it is essential that the fresh blood be immediately placed in a clean, dry tube with a minimum of manipulation; that frothing be scrupulously avoided, as the presence of foam renders the determination worthless; and that the temperature at which the blood is held, the volume used, and the diameter of the tube be kept rigidly constant.

It must be further borne in mind that coagulation is a complex reaction which involves at least two consecutive reactions (the formation of thrombin, and the reaction of thrombin with fibrinogen), and at least five factors (fibrinogen concentration, prothrombin concentration, platelet count, blood calcium content, antithrombic activity), each of which affects the result obtained. The observed coagulation time, which in human beings usually varies between three and twelve minutes, is a resultant of all these factors, and each must be considered in interpreting an unduly prolonged or unduly rapid coagulation. Finally, because most of the factors concerned in blood coagulation are normally present in large excess, it is unfortunately true that one may have a normal coagulation time despite a serious deficiency in one or more of the reagents. This is particularly true in cases with prothrombin deficiency.

2. Bleeding Time

The time during which the blood continues to flow from a sharp stab wound of the skin is the bleeding time; it is normally one to three minutes. The interpretation of a prolonged bleeding time is extraordinarily difficult. In addition to all the factors noted in the preceding paragraph which affect the coagulation time, the bleeding time is further affected by the vascularity and vascular tonus of the skin, the amount of tissue juices which mix with the blood as it oozes from the cut capillaries, and the external temperature. The coagulation time and bleeding time are used clinically to differentiate hemophilia and purpura (see below).

3. Prothrombin Content

Of much greater significance than the measurement of the coagulation time or the bleeding time is the determining of the prothrombin content of the blood. Two methods have been recommended for this purpose. In the Quick technique,[161, 162] calcium and an excess of thromboplastin are added to oxalated blood. Under these circumstances, the coagulation time will vary primarily with the prothrombin content of the blood. Small variations from the normal cannot be accurately measured by this technique, as a significant deviation from the normal coagulation time of thirteen seconds is observed only with bloods containing less than 60 per cent of the normal prothrombin content. For clinical purposes this lack of sensitivity may be of no significance, since it has been estimated that patients develop a hemorrhagic tendency only when the prothrombin falls below 20 per cent of normal.[24, 161, 162]

In the method of measuring the prothrombin content evolved by Warner, Brinkhous, and Smith[186] one determines the highest dilution of defibrinated plasma which, on the addition of calcium and thromboplastin, evolves enough thrombin to cause the coagulation of a purified solution of fibrinogen under the conditions of the test in just fifteen seconds. Although the method is clearly more laborious than the Quick technique, it apparently lends itself more readily to the measurement of small differences.

The prothrombin deficiency which occurs in cases of biliary fistula or obstructive jaundice, the explanation which has been advanced for that deficiency, and the therapeutic effect of the administration of vitamin K, have been previously discussed (page 316).

4. Purpura Hemorrhagica (Thrombocytopenic Purpura)

This condition is characterized by a decreased platelet count, which may be as low as 10,000 instead of the normal 200,000 to 300,000 per c.mm., and by a tendency to subcutaneous or joint hemorrhages. Despite the thrombocytopenia, coagulation usually occurs within normal time limits. This rests on the fact that the number of platelets normally present in blood is many times the minimum number required for coagulation. Only in extreme cases does

one observe a delayed coagulation time because of insufficient platelets. Characteristically, however, the clot remains soft, and because of the platelet deficiency, does not retract and so express serum (see page 323). Characteristically, also, the bleeding time after a sharp stab wound of the skin is greatly prolonged (Duke[45]). The reason for the purpuric tendency and the prolonged bleeding time, despite the fact that the blood may clot in vitro within approximately normal time limits, is still obscure. Normally, following a cut in the skin, thrombi form within the cut capillaries and small vessels, and act as a mechanical plug. It is probable that these platelet thrombi are deficient or absent in cases of purpura hemorrhagica. The physical character of the soft, nonretractile clot which forms extravascularly may also contribute to the prolonged bleeding time. Finally, the contractility of the vessel walls may be decreased. Whether the platelet deficiency alone suffices to allow the diapedesis of blood through the capillary walls (purpura), or whether it acts in conjunction with a damaged capillary endothelium, is an open question. Injection of antisera, prepared against platelets, causes a marked fall in the platelet count of normal animals. This is promptly followed by hemorrhage into the subcutaneous tissue. Evidence has been adduced, however, that the antibody to platelets per se does not suffice for this, but must be supplemented by some other substance present in the antisera which causes a toxic injury to the capillary endothelium.[13, 123, 166, 179]

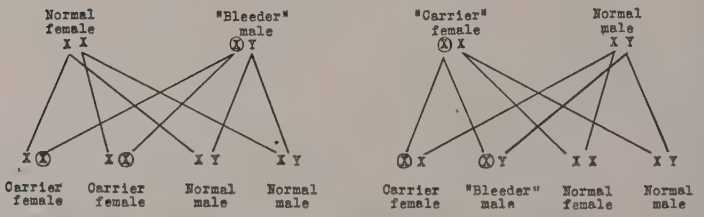
5. Hemophilia

This disease, characterized by a prolonged coagulation time and consequent tendency to bleed, is a classical example of sex-linked inheritance in man. The disease-producing gene is associated with the X-chromosome of the chromosome pair which determines sex, and is a recessive characteristic. For this reason only men are "bleeders." Women who carry the recessive disease-causing gene show no clinical evidence of hemophilia, but transmit it to approximately half their offspring. Table XI illustrates why the son of a hemophiliac is always free of the taint, and why the germ plasm of all his daughters contains the disease-producing gene as a recessive which they may in turn transmit to their offspring. Approximately half of the sons of each such "carrier" female are bleeders, and half the daughters are themselves carriers (Birch[19]).

TABLE XI

Hemophilia as a Hereditary Disease, Sex-linked and Recessive

X X and X Y represent the chromosome pair which determines sex, and ⓧ indicates the chromosome which carries the disease-producing gene



Relatively slight injury to the skin of a hemophiliac is dangerous, for in the absence of coagulation the bleeding continues unchecked. Large amounts of blood may be lost following tooth extraction, and surgical intervention is always to be dreaded. Hemorrhages into joints with resultant ankylosis are common. Paradoxically, however, despite the prolonged coagulation time and despite the tendency to hemorrhage on injury, the bleeding time as determined by a sharp stab wound of the skin is usually within normal limits. This is the reverse of the findings in purpura hemorrhagica. The normal bleeding time in hemophilia is probably to be ascribed to the fact that the blood oozing from the cut capillaries is diluted with tissue juices, which markedly accelerate the formation of thrombin.

It seems clear that the primary cause of the prolonged coagulation time characteristic of hemophilia is a delayed elaboration of thrombin. Contrary to previous reports, hemophilic blood is not deficient in prothrombin,[49, 59, 110, 162] Although many investigators[35, 110, 139, 190

have reported an excessive stability of the platelets, which presumably do not disintegrate to release the factor essential for the production of thrombin, other workers have found the platelets to be functionally normal.[46a, 49, 80, 86, 124, 151] These two observations have not as yet been reconciled. Other explanations suggested for the retarded formation of thrombin in hemophilic blood have been the presence of an unidentified inhibitor[59, 91] and a qualitative change in the plasma prothrombin.[1, 49] A promising new approach to the entire problem lies in the demonstration[13a, 126a, 151, 152, 156] that normal cell-free plasma contains a factor which is not prothrombin, and which, added to hemophilic blood or injected into hemophilic patients, causes a marked and often striking decrease in the coagulation time. It is interesting to speculate whether this factor may not be the dissolved plasma thromboplastin described by Lenngenhager,[124] which he considered primarily responsible for the activation of prothrombin to thrombin. Under these circumstances, the coagulation defect in hemophilia would simply be a quantitative deficiency in dissolved plasma thromboplastin.

6. Delayed Coagulation in the Pleural Cavity

The reputed noncoagulability of blood placed in the pleural cavity[101, 195] is as yet unexplained. Zahn and Walker[195] suggested in explanation a qualitative change in the fibrinogen; van Herwerden[96] presented evidence that an anticoagulant is released by the pleural endothelium. Denny and Minot[43] report that blood does coagulate in the pleural cavity, but that the fibrin is somehow disposed of, leaving a suspension of red cells in serum.

7. Coagulation in Vivo (Inflammation; Thrombosis); the Possible Therapeutic Use of Heparin

The coagulation caused by the intravascular injection of thrombin, trypsin, papain, or snake venoms need not concern us here (pp. 316, 326). There are, however, two types of in vivo coagulation which are of clinical significance, (1) the intercellular deposition of fibrin at foci of irritation or inflammation, and (2), thrombosis. The former may be of primary importance in walling off an affected area and preventing the spread of the toxic agent. There are several possibilities as to the nature of the stimulus responsible for this protective in vivo coagulation. It is not definitely known whether fibrinogen and prothrombin are normally present in the tissue fluids, or whether they only appear as a result of the local exudative reaction at the inflammatory focus. The fact that lymph coagulates indicates that tissue fluids contain both these factors, but lack the tissue (or platelet) derivative which initiates thrombin production. Local tissue injury and death may cause the release of this thromboplastic factor. Again, the wandering cells and leucocytes which accumulate at the focus of irritation may conceivably release proteolytic enzymes which, like trypsin, change prothrombin to thrombin, or, like papain, convert fibrinogen to fibrin directly. Finally, the mechanism concerned may differ entirely from that involved in physiological coagulation.

When a localized clot forms intravascularly at a site of operative or traumatic injury or at an area of infection, it is called a thrombus, and often contains relatively few red or white blood cells. Fresh minute thrombi consist largely of blood platelets which have adhered to the injured area and agglutinated, the thrombus growing in the direction of the blood current[144a]; it is possible that the fibrin deposit is formed secondarily, among and around these agglutinated platelets. It is reasonable to suppose that platelet derivatives liberated in concentrated form within the aggregated clump may cause the local elaboration of thrombin from prothrombin, and the local conversion of fibrinogen to fibrin. The occasional absence of red cells even in the fresh clot would be due to the fact that they are swept away by the circulating blood, and are therefore not enmeshed in the slowly-forming fibrin deposit. The laminated appearance of this fibrin results from the hydrodynamics of blood flow, as was shown by Harrison and Mason[90] in an ingenious experiment in which thrombus formation was duplicated in vitro. Heparin injected into human beings intravenously not only causes a prolonged coagulation time which persists over a period of hours,[93a] but in dogs also inhibits the formation of thrombi after chemical or mechanical injury to the vessel wall.[16a, 17, 144a, 172b] The clinical application of this observation to the prevention and arrest of postoperative thrombi has been investigated by several groups of workers,[37a, 93b, 99a, 144b] with promising results.

CHAPTER XXIX

GENERAL OUTLINE OF THE CIRCULATION

The Function of the Circulation

The function of the circulation is to carry blood to the tissues so as to maintain a proper environment for the tissue cells. This cellular or *internal environment* is the intercellular fluid which is both extravascular and extracellular; by virtue of the relative permeability of the endothelial walls of the capillaries it is in equilibrium with the blood within these vessels. A relatively constant condition of the internal environment is a prime requisite for normal existence and this is achieved by a transfer of materials in both directions across the capillary walls. The circulating blood must therefore do many things. It must carry oxygen to the tissues and remove carbon dioxide from them. It must absorb food materials in the intestine and carry them to muscles, glands and other active tissues and to depots where reserves may be stored. It must carry waste products to the kidney and other excretory glands where they may be eliminated. It must distribute heat throughout the body, moving it from the tissues where it is generated to the surfaces where it may be dissipated. It must also carry from one tissue to another those specific chemical substances known as hormones which serve to regulate the activities of various parts of the body. The internal environment is kept relatively constant largely because the slight variations which do occur, when reflected in the blood, induce compensatory reactions. These responses are set up by changes in the composition of the blood (humoral changes) acting on other parts of the body directly or indirectly by stimulation of some nervous mechanism. In this way many of the functions of the various organs are coordinated with one another to effect a physiological unity of the individual.

Of these various functions the most urgent is that of oxygen supply, since the reserves of oxygen held within the body are relatively slight. In mammals the blood is circulated by two pumps formed by the right and left sides of the heart, which force blood into a closed system of vessels arranged in two sections in series.

The pulmonary system is fed by the right heart and serves to bring the blood into contact with the alveolar air in the lungs where it may gain oxygen and lose carbon dioxide; thus *all* the blood is exposed to this contact each time it completes the double circuit. The larger or systemic circulation is supplied by the left ventricle and serves to carry the aerated blood to the various tissues of the body. It also serves all the other functions of the circulation. Here the blood flow is by no means evenly distributed; as a matter of fact an elaborate system of controls exists for the diversion of the stream to the various tissues according to their needs.

The magnitude of the simpler tasks the blood has to perform may be seen by considering the conditions in a muscle. A liter of blood can carry about 200 ml. of oxygen; under resting conditions about one-third of this is used by the muscle. The remaining two-thirds is carried back to the lungs in the

venous blood and may serve as a reserve for emergencies. The use of 60 ml. of oxygen results in the generation of about 0.3 kilogram Calorie of energy, of which about three-fourths or 0.22 Calorie appears as heat. The blood has to remove some 45 to 60 ml. of carbon dioxide together with the water formed in the process of metabolism and the heat generated. The blood has a specific heat capacity of about 0.85, so that it would be likely to leave the muscle at a temperature exceeding that of the arterial blood by about 0.26° C. With muscular work all these loads would be much increased.

Actually the situation is even more complicated, for the combination of gases with the constituents of the blood and their release in the tissues are associated with changes in free energy. According to Simonson[284] the giving off of oxygen and absorption of carbon dioxide are associated with absorption of heat, so that some of the heat generated in the tissues may be carried by the blood to the lungs as potential energy rather than as heat.

Each of the two circulatory systems (the pulmonary and the systemic) consists of a pump, the heart, a distributing arterial system, beds of fine capillary vessels and a collecting system of veins. Through the capillaries the blood percolates at a relatively slow speed so as to allow exchange of gases, water, electrolytes, and other diffusible substances between the blood and the tissues. The capillary vessels must individually be short, so that the time of circulation is not unduly lengthened. The remaining vessels serve as distributing and collecting channels, and to some extent also as blood reservoirs.

The Heart as a Pump

The pumping action of the heart may be watched in a mammal with an opened thorax and with the pericardium removed. The heart continues to contract, if asphyxia be prevented by rhythmical distention of the lungs with air. Its action may be followed even more readily in cold-blooded animals, such as the frog or turtle, for the movements of such hearts are slower and continue even in the absence of all respiration. Contraction (known as systole) may be seen to originate at the junction (known as the sinus venosus) of the large veins with the auricles; it spreads to the auricles and from them to the ventricle or ventricles. Ventricular contraction is associated with blanching and hardening of the ventricle, followed by a diminution in its size. The auriculo-ventricular groove moves downward towards the apex, which does not move upward, but only forward, while the ventricle also rotates slightly. The failure of the apex to move upward is the necessary consequence of the thrust imparted to the moving column of blood. To this thrust there is a recoil (as in a gun) which forces the apex downwards. The forward movement of the apex and the rotation of the heart depend on the tendency of the curved aortic arch to straighten as it is distended with blood. As the pressure falls during the ventricular relaxation (known as diastole) these movements are reversed. It was on such observations, as well as on inspection of the veins, that Harvey in 1628[161] built his theory of the circulation of the blood. In doing so he had to assume the existence of capillaries joining the arterial with the venous systems of vessels both in the lungs and in the tissues. The existence of these capillary vessels in the lungs was first demonstrated by Malpighi in 1661. With the evolution of the microscope Leeuwenhoek in 1668 was able to watch the flow of blood through the capillaries in the web of the frog's foot.

William Harvey showed (1) that the heart ejects blood: "The heart contracts all over but particularly the sides, so that it looks longer and narrower; it feels harder. When the heart moves it is paler in color, but when it pauses it is of a deeper blood color. At the instant the heart contracts in systole and strikes the breast, the arteries dilate, give a pulsation, and are distended. In arteriotomy the blood is squirted alternately far and near, the greater spurt coming with the distention of the artery at the time the heart strikes the ribs. This is the moment the heart contracts, and it is by this motion that the blood is ejected." He showed (2) that the blood flows in the veins toward the heart: "Fabricius" (Harvey's teacher) "first described membranous valves in the veins. The valves are present solely that blood may not advance from the center of the body into the periphery through the veins, but rather from the extremities to the center. This fact may be more clearly shown by tying off an arm of a subject as if for blood letting." (*AA*, Fig. 99, *1*.) "There will appear at intervals (especially in rustics) knots or swellings (*B, C, D, E, F*) not only where there is branching but also where there is none. These are caused by the valves. If you will clear the blood away from a nodule or valve by pressing a finger below it" (*II*, Fig. 99, *2*) "you will see that nothing can flow back, being entirely prevented by the valve. If you will press downwards against the valve O, you will note that nothing can be forced through it. From many such experiments it is evident that the function of the valves in the veins is the same as that of the three sigmoid valves placed at the opening

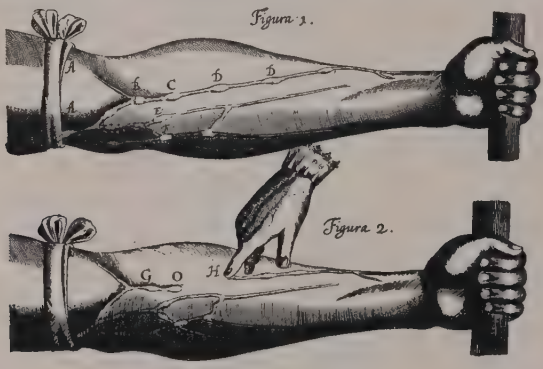


Fig. 99.—Figures 1 and 2 from William Harvey's presentation of experiments on venous flow. Description in text.

of the aorta and pulmonary artery, to prevent, when they are tightly closed, the reflux of blood passing over them." He showed (3) that to assume that blood passes from the big veins through the lungs back to the heart is reasonable: "If only anatomists were as familiar with the dissection of lower animals as with that of the human body, all these perplexing difficulties would, in my opinion, be cleared up. The situation is first of all clear enough in fishes where there is a single ventricle and no lungs. It is not hard to see the same thing in other animals with but a single ventricle, such as toads, frogs, serpents, and lizards. They have lungs of a sort. It is obvious in opening these animals that the blood is transferred from the veins to the arteries by the heartbeat. Since there are more animals without lungs than with them, it may be concluded that for the majority of animals an open way exists for blood to pass through the cavity of the heart from the veins to the arteries. The same thing is very apparent in the embryos of animals possessing lungs. In the more perfect warm-blooded animals, as man, the blood passes from the right ventricle through the pulmonary artery to the lungs, from there through the pulmonary vein into the left auricle, and then into the left ventricle. That there is nothing to keep this from being so, is evident when we consider how water filtering through the earth forms springs and rivers, or when we speculate on how sweat goes through the skin or urine through the kidneys." He demonstrated (4) on quantitative grounds that the output of blood from the heart must be so great that a circulation provides the only possible explanation: "Let us consider that

the left ventricle when filled in diastole contains 2 or 3 ounces. In a cadaver I have found it holding more than 3 ounces'' (85 ml.). ''Let us consider how much blood it forces into the aorta with each contraction. As a reasonable conjecture suppose a fourth, fifth, sixth or even an eighth part is passed into the arteries. Then we may suppose in man that a single heartbeat would force out either half an ounce, three drams, or even one dram of blood. The heart makes more than 1000 beats in a half hour, in some 2000 or even 4000. Multiplying by the drams there will be in half an hour either 3000 drams, 2000 drams, 500 ounces or some other proportionate amount of blood, but always a greater quantity than is present in the whole body.''

These excerpts from Leake's translation of Harvey's book have been given as an illustration of the technique of physiological investigation so well illustrated in Harvey's work, namely: careful anatomical and physiological observation with a view to relating structure and function; comparative physiological and anatomical study to determine the general principles involved; and the use of data, even if inaccurate, to determine whether suggested explanations fall within the range of quantitative possibilities.

Harvey's discoveries concerning the events of the cardiac cycle led him to assume that the degree of emptying of the heart varies. The acceptance of the theory of the circulation allowed more precise estimation of the probable volume output of the human ventricle, and on the basis of wax casts the stroke volume was assigned a value of 3.276 cubic inches (54 ml.) by Stephen Hales[151] in 1733. This estimate compares favorably with the modern estimation of some 60 ml. Modern advances have, however, developed a better understanding of the factors involved, through the use of instruments capable of measuring intracardiac pressure and of determining the time relations of the changes involved.

The data now available indicate that the heart of an average man at rest ejects about 60 ml. for each stroke of each ventricle. At a pulse rate of 65 the blood is then circulated at the rate of 3.9 liters per minute. In a middle-aged subject of average size (age 30 and surface area of 1.75 square meters) the aorta may be expected to have a diameter of 1.86 cm. and a cross sectional area of 2.7 $cm.^2$ The mean velocity in the aorta must, therefore, be of the order of 24 cm. per second. During activity it is many times greater.

The Capillary System

The walls of these vessels are formed by thin endothelial cells unsupported by muscular or elastic tissue. The cells, or the interstices between them, are freely permeable to water, salts, and organic solutes of low molecular weight as well as to oxygen and carbon dioxide. Thus a free exchange of these materials is assured. However, whole blood is not free to escape, for the walls are normally impermeable to the blood cells (except the leucocytes under special conditions) and to the large colloidal particles of the plasma proteins. The latter, therefore, exert an osmotic pressure; water and salts diffuse into the capillary vessels until these vessels are distended by a hydrostatic pressure which equals this colloidal osmotic pressure. At this pressure level outward flow due to filtration balances inward flow due to colloid osmotic pressure. Under normal conditions in man the osmotic pressure of the proteins is of the order of some 25 mm. of Hg. The hypothesis that this balance underlies fluid transfer between the blood in the capillaries and the tissue fluids was originally advanced by Starling[286] and is consequently known as the Starling hypothesis. Much experimental evidence attesting its validity has been attained. Owing to this balance the *average* pressure in the capillaries must remain at a level determined by the balance between osmotic and hydrostatic pressures. This is true even if blood flow ceases, provided that the capillary wall is undamaged

and its normal impermeability to proteins is retained. If blood be flowing there is a gradient of hydrostatic pressure along the vessels with pressures both above and below the level of balance. The conditions of balance then depend on the differences in colloid osmotic pressures of the blood and the tissue fluid on one side, and hydrostatic pressure on the other. Values likely to prevail are indicated in Fig. 100.

Through the capillary vessels the blood flows with an average velocity of about 0.5 mm. a second. Since the capillaries are only about 0.5 mm. in length, the capillary circuit is completed in about 1 second. This is very slow compared to the flow of 24 cm. a second found under similar conditions in the aorta. The reduction in the velocity depends on the broadening of the stream in the distributing system, just as the velocity of flow in a river bed is reduced

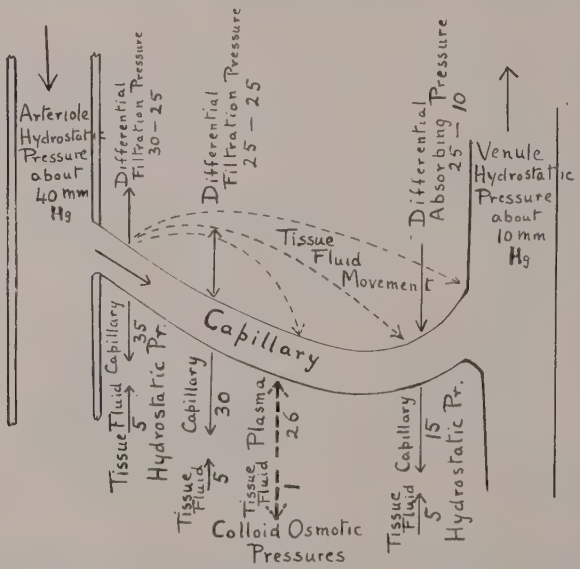


Fig. 100.—A capillary carrying blood from an arteriole to a venule is represented diagrammatically. Below it are indicated the colloid osmotic pressures of the tissue fluid (1 mm. Hg) and of the capillary blood (26 mm. Hg); these are opposed forces and at all points along the capillary the resultant force of 25 mm. Hg tends to cause movement of water and noncolloid solutes into the blood. Below the capillary are also indicated the hydrostatic pressures of the tissue fluid (represented as 5 mm. Hg everywhere) and of the capillary blood (35 to 15 mm. Hg); these pressures also exert opposed effects on fluid transfer across the capillary endothelium. At all points near the arteriole the difference, though grater proximally than distally, favors transfer of fluid from capillary blood to tissue fluid. The actual transfer at any point depends on the difference between the sum of the two pressures tending to force fluid out of the capillary and the sum of the two pressures tending to force fluid into the capillary blood. Three of these differential pressures are indicated above the capillary. It can be seen that the hydrostatic pressure of the tissue fluid must be slightly higher around the arteriolar end than around the venous end and consequently there is some fluid movement in the direction of the arrows.

in the broader parts of its course. In the circulatory system this widening of the total bed depends on the character of the branching of the vessels. Although each branch is smaller than the parent vessel, the sum of the cross-sectional areas of the branches is greater than the cross-sectional area of the parent vessel. Since the volume of the blood flowing in a closed circular system remains the same, the total cross-sectional area of the capillary bed may be

calculated. Thus, with the figures for man already assumed the total cross-sectional area of the capillary bed must be $2.7 \times \frac{24.0}{0.05}$ or 1296 cm.^{2} (cross-sectional area of the capillaries = cross-sectional area of aorta × average velocity in aorta/average velocity in capillaries). If the capillaries have an average length of 0.5 mm., the volume contained within them is 64.8 ml. The capillaries are not all patent in a subject at rest, and the value given merely approximately represents the active capillaries. The volume contained in all the capillaries, if dilated simultaneously, is probably many times (10 to 15) larger.

The change from the relatively rapid average velocity in the aorta of about 24 cm. a second to the low velocity in the capillaries is not made abruptly. The velocity is gradually reduced in the system of *distributing* arteries. The total cross-sectional area is progressively increased in these vessels as they divide into smaller branches. Similarly in the *collecting* system of veins, which transmits blood from the capillaries to the heart, the total cross-sectional area of the veins is progressively reduced, so that the velocity of flow is increased. The total cross-sectional area of the veins is much larger than that of the arteries, and at the entrance to the heart the total area of the two venae cavae is approximately double that of the aorta, so that the average velocity within them in the conditions under discussion must be about 12 cm. a second.

The Distributing System: The Arterial Tree

This system at its commencement in the aorta gives rise to large branches, which though smaller individually than the parent vessel have a total cross-sectional area which is approximately the same; (according to Hess[169] the ratio of the sum of the cross-sectional areas of the primary branches to that of the aorta is 1.24 in a child of three months, 1.02 in early adult life, and 0.95 after the age of forty). Consequently the average rate of blood flow within these larger vessels remains approximately the same as in the aorta. The condition is very different in the more peripheral branches.

The relationships of the peripheral vessels may be realized more readily by detailed consideration of a single area. A careful histological study of the distribution of the mesenteric artery in a dog of 6 kg. weight was made by Mall, and his data have been carefully analyzed by Schleier.[273] These data are presented in Table XII. In this table the rapid broadening of the stream and the consequent effect on the velocity of blood flow (calculated by Schleier on a basis of a capillary flow of 0.5 mm. a second) is clearly indicated. It may be noticed that the velocity remains relatively high in the larger arteries of group *a* and that the main reduction is in the smaller branches of group *b*. The rate of flow is probably that characteristic of resting conditions; it represents a flow of 40 ml. per minute in this system, whose total volume, according to this histological analysis, is 16.84 ml. This implies that the blood completes the mesenteric circuit in about twenty-four seconds. The time occupied by the blood in completing the whole circuit (including the heart and lungs) would be 30 to 45 seconds.

The distributing vessels have important functions beyond that of simple conduction. The larger primary branches act as an elastic reservoir, and have walls consisting largely of elastic tissue and smooth muscle. The reservoir

action allows them to accommodate the blood ejected in systole and to store much of the energy of systole which is then expended to maintain a circulation during diastole. The action has been compared to that of an air-chamber reservoir in a wind instrument, such as a bagpipe. It has been called the "Windkessel" effect by the Germans.

Blood flows from the heart through this distributing system as the result of the free energy imparted to the blood by the heart. This free energy exists mainly as pressure energy developed through the stretching of the elastic system but also to some extent as kinetic energy. Under resting conditions

TABLE XII

CHANGES WHICH TAKE PLACE WITH BRANCHING OF THE MESENTERIC ARTERY OF A DOG
(Modified from Schleier[273] after Mall)

	TOTAL NUMBER	RADIUS (CM.)	TOTAL CROSS-SECTIONAL AREA (CM.^{2})	LENGTH (CM.)	MEAN VELOCITY (CM./SEC.)	PRESSURE FALL (MM. HG)	PRESSURE FALL PER 1 CM. LENGTH (MM. HG)
a. Mesenteric artery	1	0.15	0.07	6.0	16.80	0.8	0.13
Main branches	15	0.05	0.12	4.5	10.10	3.2	0.72
End branches	45	0.03	0.13	3.91	9.30	7.4	1.88
b. Short and long intestinal branches	1,899	0.0068	0.20	1.42	5.80	23.5	16.55
Last branches	26,640	0.0025	0.57	0.11	2.10	7.2	65.50
Branches to villi	328,500	0.00155	2.48	0.15	0.48	5.4	36.00
Arteries of villi	1,051,000	0.00122	4.18	0.20	0.28	8.1	40.40
c. Capillaries of villi	47,300,000	0.00040	23.78	0.04	0.05	2.4	58.80
Total fall in pressure						*58.0*	
d. Veins at base of villi	2,102,400	0.00132	11.59	0.10	0.10	1.03	10.28
e. Veins before entering submucosa	131,400	0.00375	5.80	0.10	0.20	0.29	2.94
Last branches of submucosa	18,000	0.0064	2.32	0.15	0.51	0.37	2.44
Last branches of short intestinal veins	28,800	0.0032	0.93	1.1	1.30	2.50	2.27
Long and short intestinal veins	1,899	0.0138	0.84	1.42	1.40	1.40	0.99
f. Last branches of mesenteric vein	45	0.075	0.79	3.91	1.50	0.22	0.06
Branches of mesenteric vein	15	0.12	0.67	4.5	1.70	0.07	0.02
Mesenteric vein	1	0.3..	0.28	6.0	4.2	0.05	0.01
Total fall in pressure						*5.93*	

the latter plays a small part and for the present the energy available to move the blood may be considered simply as pressure energy. Frictional transformation of free energy into heat develops as the viscous blood moves through the vessels, so that the resistance to flow may be measured by the loss of pressure head. Such pressure falls were calculated by Schleier on the basis of normal values of blood viscosity and the rates of flow already discussed. The figures obtained are given in Table XII. The values are probably fairly correct except in the case of the smaller vessels where complexities dependent on the suspension of corpuscles in plasma make the estimation of the effective blood viscosity inaccurate. There is clearly little loss of energy in moving blood through large vessels such as the aorta and little even in vessels as small

as the branches of the mesenteric artery (group *a* in the table). The muscular coat of these large vessels can consequently have little effect in varying resistance and regulating blood flow. Yet active contractions do occur and induce variations in elastic properties of these reservoirs, as well as in the amount of blood contained within them.

The smaller branches of the arterial tree, such as those included in group *b* of Table XII, are, on the other hand, very narrow and offer a considerable resistance to flow. Though much broader than the capillaries they are also very much longer, so that frictional losses are great. These vessels have highly developed muscular coats and less elastic tissue. While they act as part of the elastic reservoir, their main function is to control, by their degree of constriction, the resistance to flow. A change in their diameter can shunt the blood flow from one area to another, according to the needs of the moment. The greater fall of pressure is found, therefore, in these vessels. The average capillary pressure, as has already been stated, is determined by the conditions of fluid balance; it is about 30 mm. Hg. Since the average pressure in the aorta is normally 80 to 90 mm. or more, the pressures which are necessary according to Schleier's calculations are available.

The Collecting System: The Veins

The characteristics of the collecting system may also be gauged from Table XII. There are first small venules *(d)*, the walls of which are very thin and have little supporting tissue. These vessels probably assist the capillaries in the exchange of materials between the blood and the tissues. The hydrostatic pressure within these venules is usually below the colloid osmotic pressure, so that an inward flow of fluid characterizes their normal state. They may be particularly important in the absorption of water and diffusible substances into the blood. They are succeeded by intermediate veins *(e)*. These are much broader vessels than the corresponding arteries, so that the velocity of blood flow is less, and the same volume of blood is carried with a very small fall in pressure head. This fact is important, for in a condition of complete muscular relaxation the pressure head available to return blood to the heart is limited to the 30 mm. Hg (approximately) difference between the pressure in the capillary and that in the right auricle. Under normal conditions cardiac activity exerts only minor effects on this pressure head, for a change in the average capillary pressure can be attained only after adjustments in fluid balance. Under normal conditions the gradient is adequate if the subject be lying down, since the large venous channels offer so little resistance. In the standing position it is quite inadequate and other mechanisms come into play.

The Pressure Gradients

The pressure gradients calculated by Schleier on theoretical grounds approximate closely those observed experimentally. The pressures found in the mesenteric vessels by Landis[210] are shown in Fig. 101 where, however, the values are plotted in centimeters of water (they may be converted to mm. Hg, for comparison with figures previously used, by dividing by 1.36). In mammals (anesthetized) the pressure in the aorta was 71 to 81 mm. Hg, while the capillary and colloid osmotic pressures balanced at 16 to 21 mm. Hg. The fall

of pressure in the system resembles that represented in Table XII but the rate of fall is less in the arterioles and greater in the capillaries.

The gradients are maintained by the heart action, and in its absence the pressures throughout the system tend to approach one another. They do not fall to zero (the atmospheric level) but to about 15 to 20 mm. Hg, a level determined by the colloid osmotic pressure of the plasma (somewhat lowered by dilution with tissue fluid). This may be readily seen in animals if blood flow be stopped by clamping the venae cavae or by causing a prolonged inhibition of cardiac activity by vagal stimulation. Arterial pressure falls and venous pressure rises as the arteries empty into the capillaries and the capillaries empty into the veins. As the pressure levels approach that at which fluid balance is maintained in the capillaries, they tend to stabilize, but a real equilibrium is never attained. Oxygen lack soon damages the capillary wall so that the plasma proteins are no longer retained.

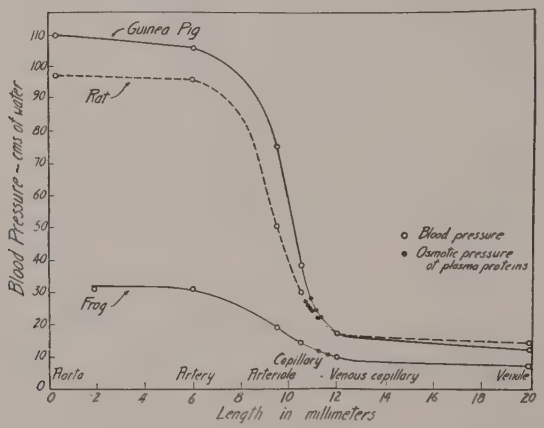


Fig. 101.—The pressure fall in the peripheral vessels of the rat, guinea pig, and frog (mean pressures). The closed circles indicate the range of the osmotic pressures of the plasma proteins in each case. (After Landis: Physiol. Rev. **14**: 404, 1934.)

If the heart be allowed to resume activity before this damage becomes irreversible, its action empties the large veins into the arterial system. Thus at one and the same time the heart lowers the venous pressure below the level of the colloid osmotic pressure and distends the arterial system, raising the pressure within it.[286] By raising the aortic pressure, the heart action maintains a pressure gradient from the aorta to the capillaries and thus induces a flow in the distributing system; it lowers the pressure in the central veins and so creates another pressure gradient from the capillaries to the veins, which generates a flow in the collecting system. The average capillary pressure may be considered the reference point of the system. If this pressure falls slightly, tissue fluid passes into the system, and blood volume is increased until a balance is regained through lowering of the colloid osmotic pressure by dilution. The pressure at which balance is attained is thus dependent on the total amount of blood protein available and the volume of the vessels to be filled.

The Volumes of the Vessels

The volume of the whole closed system of vessels, including the pulmonary circulation, must obviously be the same as that of the blood. A vacuum in such a system is impossible. Little is known as to the relation of the volumes of the different vessels to one another in man. The data on the mesenteric vessels of the dog, given in Table XII, indicate the relationships of the volumes of different parts of this system to one another. Thus the blood contained in the arterial portion (*a* and *b*) represents 21 per cent of the total; it is about equally distributed in the larger and smaller of these vessels. The capillaries and venules together (*c* and *d*) account for only an additional 13 per cent, while 66 per cent of the total is contained in the collecting veins (*e* and *f*).

The veins contain a large proportion of the blood, and must have an important function as blood reservoirs. They have definite muscular coats which are particularly well developed in the veins of the portal system. When the veins are reduced in size by contraction of this coat, a large volume of blood must be made available for use in other areas. Any constriction must, however, increase the resistance to flow and cause an increased pressure gradient along the vessels, unless it is associated with a simultaneous reduction in the rate of blood flow.

The Nature of the Control of the Circulation

The circulation has to be controlled, not only to maintain an adequate supply of oxygen and food for active tissues, but also to effect an adequate transfer of heat. The principles of the circulation are simple, but the regulation of the circulation to meet the demands made upon it introduces many complexities. The blood must be distributed differentially along various alternate paths according to the demands of different tissues. These adjustments have to be attained without serious disturbances in the average level of capillary pressure, which, if long maintained, would result in abnormalities of fluid distribution. They must also be attained without any sudden considerable change in blood volume. In addition, adjustments have to be made to overcome the considerable pressures created by gravity, and safeguards have to be provided to prevent the pump from being overstrained. This complex control is partly attained by carefully balanced reflex effects, partly by the action of chemical substances on the vessels, and partly by physical effects, such as the balances between filtration and osmotic pressures which have been described.

CHAPTER XXX

THE HEART

The heart by its mechanical activity causes circulation of the blood. This is its sole function. The rhythmical mechanical contraction is initiated by a process of excitation, which arises in the heart itself. The mammalian heart is not a simple organ, but consists of four chambers, capable of independent activity but so closely interrelated anatomically that they work as a coordinated whole.

STRUCTURE OF THE HEART

Heart Muscle.—The gross anatomy and histological structure of mammalian heart muscle need not be reviewed here, but certain main principles must be kept in mind. Cardiac muscle consists of cross-striated fibers, capable of more rapid contraction than smooth muscle but incapable of contracting with anything like the speed of skeletal muscle. The muscle fibers are branched and so connect together as a large syncytium in which activity spreads readily from one cell to another. In the mammalian heart six muscle bands have been described (Mall; Sands Robb[259]); these muscle bands are common to both chambers (see Figs. 109 and 110). While the two ventricles are intimately connected with each other by these muscular bands, they are separated from the auricles by a strong fibrous ring across which the only functional junction is made by the auriculo-ventricular bundle.

In the auricles the muscular structure resembles that of the ventricles but the walls are much thinner and there is little definite differentiation of the musculature into anatomically recognizable bands. The two auricles and the interauricular septum are intimately connected with one another just as are the ventricles.

Specialized Conducting Tissue.—In the more primitive hearts of the lower vertebrates, in which the structure is simpler, the large cephalic and caudal veins on either side join, and the vessel produced by the fusion passes medially to meet the similar vein formed on the other side. The fused combination of all four veins forms a chamber, the sinus venosus, in which the heart contraction commences. In species with a slow pulse, such as the frog, turtle or snake, particularly if the heart activity is slowed by cooling, contraction may be seen by the naked eye to spread from the sinus venosus to the auricles, and so to the ventricles. Histological study indicates that this spread must be through the muscle fibers unless it passes through nervous tissue; no other specialized tissue is present in the hearts of these more primitive species. As the heart becomes more differentiated, develops four chambers and achieves in some forms a much greater size (the heart of a whale may weigh as much as a whole man), a special band, the *auriculo-ventricular bundle,* connects the auricle and ventricle. This band consists of special muscle fibers, the Purkinje fibers. It

starts in the *auriculo-ventricular node,* a mass of more primitive cardiac muscle tissue, which represents in the adult mammalian heart the primitive left sinus venosus. It is situated close to the entrance of the coronary sinus into the right auricle. The auriculo-ventricular bundle passes forward and downward to the interventricular septum, where a little in front of the attachment of the septal cusp of the tricuspid valve, it bifurcates into right and left branches, which run down each side of the septum immediately beneath the endocardium (see Fig. 102). Each main branch ultimately divides up into an intricate system of smaller branches, which become reflected over the inner surface of the ventricles. Both main branches send a liberal supply of twigs to the papillary muscles. These special fibers are surrounded by a fibrous sheath, have a liberal supply of blood vessels and lymphatics and contain a high percentage of glycogen.

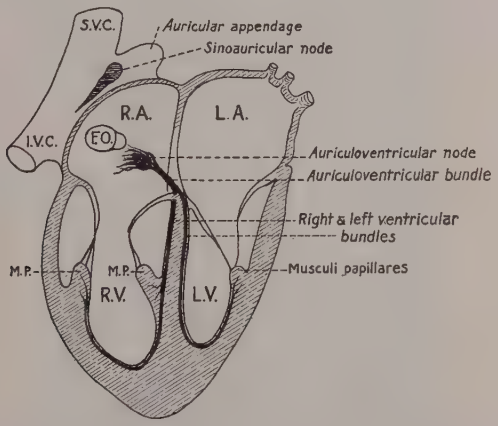


Fig. 102.—Diagram to show the general ramifications of the conducting tissue in the mammalian heart. The right and left auricles and ventricles, the superior and inferior venae cavae are indicated. F.O. indicates the position of the foramen ovale.

The priority of the discovery and recognition of the peculiar structure and essential nature of the cells of the *auriculo-ventricular node* should be ascribed to Stanley Kent (1892). In 1893 W. His, Jr.[175] studied the anatomy and physiology of the auriculo-ventricular node and bundle and its branches, and this connecting tissue is, in consequence of his intensive study, universally known as the *auriculo-ventricular bundle of His.* Kent[200] showed that all other connections between the auricle and ventricle are fibrous in character, except one in the right margin of the heart, but it is doubtful whether this additional muscular band plays any part in conduction from auricle to ventricle.

In 1907 a mass of cardiac muscle, with fusiform fibers of embryonic type, was discovered by Keith and Flack[198] in that part of the auricle which corresponds anatomically to the right sinus venosus of the heart of cold-blooded vertebrates; it lies in the sulcus terminalis just below the fork formed by the junction of the upper surface of the auricular appendix with the superior vena cava. *The sino-auricular node,* as it is called, is shown in Fig. 102; it is not definitely connected with the auriculo-ventricular node by any specialized tissue. Near the node the muscular fibers of the auricle spread out in a fan-

shaped manner from a point called by Lewis[220] the concentration point. According to Eyster and Meek[110] the spread of excitation to the auriculo-ventricular node is preferentially along direct muscle fasciculi, which connect the two nodes.

FUNCTIONAL PROPERTIES OF CARDIAC MUSCLE

The mechanical changes may be readily demonstrated on the heart of a cold-blooded vertebrate, such as the frog or turtle.

All-or-None Law.—Because of the branched arrangement of cardiac muscle a stimulus applied to the heart causes a contraction of all the fibers or none, and the magnitude of the response does not vary with the strength of the stimulus (see page 16). This does not imply that the strength of a contraction is always the same. It means that all the fibers respond and the contraction is maximal for the condition, chemical and mechanical, of the heart at the time. As will be seen later, both the chemical environment and the degree of initial stretch of the fibers are factors which exert powerful influences on the strength of the contraction. The essence of the all-or-none law is that although many factors may influence the strength of the response, the strength of the stimulus is not one of these.

Refractory Period.—During a contraction the heart is said to be "refractory" in that it does not respond to an electrical or other stimulus applied at this time. This prolongation of the refractory period is characteristic of cardiac muscle and stands in striking contrast to the condition in skeletal muscle (see page 21). It should be noted that the electrical changes are also prolonged throughout systole. During contraction the refractory state is absolute; no stimulus, however strong, is effective. During relaxation the excitability is subnormal and is gradually built up till it reaches the normal level at about the start of the next spontaneous beat. During this relatively refractory state the heart will contract prematurely if excited by a sufficiently strong stimulus. If a series of strong stimuli are given to the ventricle of the beating frog or turtle heart, those arriving during systole will produce no effect, others arriving in the relatively refractory period produce premature contractions. Such contractions last long enough to make the ventricle refractory to the normal stimulus transmitted by the auricle in the next beat, which, therefore, fails to affect the ventricle, and a *compensatory pause* is seen; the ventricle resumes the normal rhythm of the heart with the following beat. The apparent height of the induced extrasystole varies somewhat. The extrasystole may even appear to have a height exceeding that of a normal contraction, but this is an artifact due to the fusion of the contraction with a greater or less degree of auricular activity. The fundamental rhythm of the pacemaker is not readily affected by such stimulation even when electrical spread to the sinus occurs, though the rate of development of tension in the auricle may be accelerated. The method of recording may be arranged to give mainly a picture of ventricular events (Fig. 103) or the whole heart may be allowed to affect the lever and the curves be subjected later to analysis.[290]

A quiescent heart muscle preparation may be obtained in the amphibia either by using the apical part of the ventricle alone, or by inducing quiescence in the heart as a whole by means of the "Stannius" ligature. This ligature consists of a heavy thread tied round the white crescentic line which marks in the frog and

turtle the junction of the sinus venosus with the auricle. This area is richly supplied with vagal fibers, and the ligature is assumed to produce quiescence by the irritation of these nerves by mechanical injury. When a stimulus is applied to such a quiescent heart a contraction is induced, and the heart is rendered refractory in a manner quite similar to that of a spontaneous contraction. After the relatively refractory period a stage of supernormal excitability, relative to the quiescent condition, may be seen (compare that in nerve, Fig. 16, page 22), particularly if the heart is supplied by a somewhat acid solution (the mechanical change may also be greater than normal in a response to such stimulation[4]).

Absence of Tetanus.—Since the absolutely refractory period lasts throughout contraction, a second stimulus cannot be effective during a contraction, and the fusion of two or more contractions into a tetanus is impossible (contrast

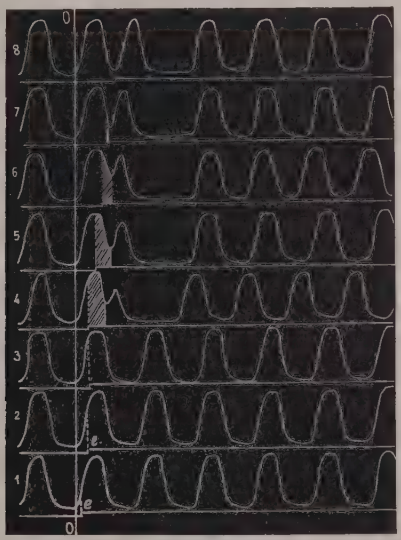


Fig. 103.—Myograms of frog's ventricle, showing effect of excitation by break induction shocks at various moments of the cardiac cycle. The line *O* indicates the commencement of all the beats during which the shock is sent in. It will be noted that in *1*, *2*, and *3*, the heart is refractory to the stimulus. The signals indicate the moments at which the stimuli were applied. From *4* to *8* the heart reacts by an extrasystole, after a delay, which is progressively less the later in diastole the stimulus enters, as shown by the sections shaded obliquely to make them more conspicuous. The extrasystoles increase in height from *4* to *8*, each being followed by a compensatory pause. (From Luciani's *Human Physiology.*)

skeletal muscle, page 20). As was pointed out by Mines,[241] the character of the response is determined by the previous history of the heart. On the quiescent preparation this dependence may readily be demonstrated. The refractory period associated with a single response following a long period of rest is long. If, however, a series of stimuli are given at steadily shorter intervals, the contractions become smaller, relaxation is less complete, and the heart is able to follow a rate of stimulation far more rapid than was originally possible.

Staircase.—This term has been given to a factor varying the size of the cardiac response which is commonly in evidence. If after a period of prolonged rest the quiescent heart be stimulated at a regular but slow rhythm

(e.g., once in two seconds) the resulting contractions will be found to become regularly more forcible in the initial series of beats, so that a sort of staircase appearance is produced in the records. This is apparently due to some favorable chemical change following stimulation, the character of which is not known.

Effect of Initial Tension.—By far the most important of the factors causing variations in the strength of contraction is the initial length of the fibers, which varies with the initial tension. In an organ such as the heart, where the fibers are arranged more or less circularly around a central cavity, both the initial length and tension of the fibers depend on the degree to which the cavity is filled. The property of muscle to contract more forcibly when subjected to an initial stretch is a general property of muscle (for skeletal muscle see page 19). The heart utilizes this property to vary the force of its contraction. As will be seen later the initial tension has also a marked effect on the oxygen usage of the

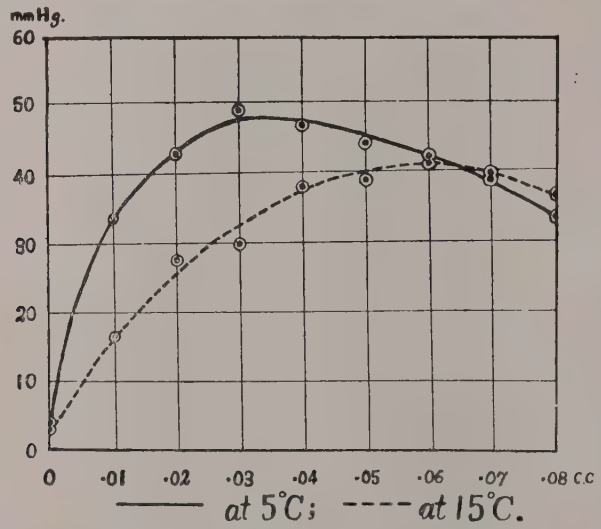


Fig. 104.—Relation between tension (ordinates) developed by a frog heart contracting isometrically and its initial contained volume (abscissae). Curves representing data at 5° and at 15° are shown. (From Doi: J. Physiol. 54: 218, 1920.)

heart. The effect of this important factor on the strength of contraction is demonstrated in Fig. 104 in which the volumes contained by a frog heart in diastole are plotted as abscissae, and the pressures developed in an isometric contraction (without expulsion of fluid) as ordinates. The diastolic pressures, which corresponded with the various diastolic volumes shown, varied from 0 to 6 mm. Hg. It is evident that the tension developed at 15° C. was greater with increasing initial stretch up to a volume of 0.06 ml.; at a lower temperature the optimal stretch was less. This property enables the isolated heart to adapt itself not only to an increased venous filling but also, as will be seen later, to an increased arterial resistance. This behavior was demonstrated by Starling on the mammalian heart-lung preparation, and consequently the capacity of the heart to vary the work it performs through alterations in its diastolic volume is known as *Starling's Law of the Heart.*

ORIGIN AND CONDUCTION OF HEARTBEAT

The rhythmic contractility is not dependent on the central nervous system, for the excised heart continues to beat. It might be dependent on transmission to the muscle fibers of impulses generated in peripheral nervous tissue; such is the *neurogenic* hypothesis. On the other hand, it might originate directly in the muscular tissues of the heart, and peripheral nervous structures and central connections might serve merely as part of the regulating mechanism; such is the *myogenic* hypothesis. No final decision as to which of these two hypotheses is the correct one can be given, though the myogenic theory is the more generally accepted one.

Neurogenic Hypothesis.—In favor of this hypothesis the following evidence may be advanced:

1. The heart of the primitive king crab, Limulus, consists of a sacculated organ, along which runs longitudinally a ganglionated nerve cord. This cord gives off fibers which go to the heart and also to two lateral nerve cords (Fig. 105). Removal of the central cord is followed by the total abolition of the heartbeat. In this primitive animal the rhythm is undoubtedly of nervous origin (but this does not justify the assumption that the same thing is necessarily true in other animals). The properties of the Limulus heart closely resemble those of the vertebrate heart.

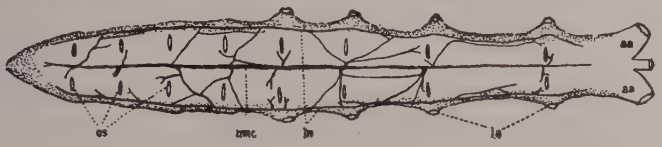


Fig. 105.—Heart and cardiac nerves of *Limulus polyphemus* (Carlson). *aa,* anterior arteries; *la,* lateral arteries; *lm,* lateral nerves; *mnc,* median ganglionic chain; *os,* ostii or afferent stomata, each pair of which corresponds to one of the segments into which the Limulus heart is divided.

2. The disposition of the nervous structures in the heart of the frog and turtle corresponds exactly with the development of rhythmic power in different parts of the heart; the latter is greatest in the sinus and least at the tip of the ventricle. (Against this interpretation it may be argued that, if the rhythm were of muscular origin, regulatory nerves would naturally be distributed chiefly to the point at which the rhythm originated.)

Myogenic Hypothesis.—The following are outstanding arguments in favor of this hypothesis:

1. The heart beats in the embryo chick before any nerve cells have grown into it, and parts of the heart muscle isolated from such embryos artificially and placed in blood plasma continue beating for days. Embryonic heart muscle, therefore, certainly has this rhythmic capacity, though this does not necessarily mean that the same power is preserved in fully developed muscle cells.

2. The nervous structure of the heart may be damaged mechanically without interfering with rhythmic contraction. Also, administration of atropine paralyses the postganglionic fibers of the vagus without interfering with the rhythmic properties.

3. The apex of the ventricle in the turtle heart contains no nerve cells and normally does not show a spontaneous rhythm. If, however, such a nerveless piece of heart muscle is perfused under pressure, and if a contraction be initiated by electrical stimulation or adrenalin, it may continue to contract rhythmically.

The Fundamental Stimulus.—The investigations of R. S. Lillie on excitatory processes, particularly in relation to conduction in nerve, have focussed attention on the properties of surface membranes and polarization (see page 50). Lillie[221] has produced an iron wire model with a polarized surface. This can under certain circumstances generate a spontaneous rhythm of alternating

depolarization and polarization. Some such sequence is likely to be the cause of the cardiac rhythm. One may, therefore, think of an area in which surface polarization is gradually developed but ultimately becomes unstable; the resulting breakdown generates an electrical current which causes instability in other areas. The whole process would thus depend on the permeability of the membrane and on ionic concentrations inside and outside the cells. In favor of such an hypothesis is the close dependence of the cardiac rhythm on the ionic concentrations of the fluid bathing the heart.

Essential Inorganic Ions.—An excised heart continues to beat if kept in a balanced solution of salts. Even a mammalian heart will beat for hours, if it be kept warm and supplied with oxygen by perfusing the coronary arteries with oxygenated saline. While potassium is essential for normal cardiac activity, an excess of this element in the fluid supplied to the heart causes a slowing and finally a stoppage of the heart in relaxation. The effect is reversible, and the heart resumes its rhythm on return to a more normal solution. Hofmann[178] found that an increase of potassium to 0.092 per cent KCl in Ringer's solution causes cessation of the beat in perfused rabbit hearts. Lowering the potassium concentration causes a more rapid rhythm, but if the potassium content is very low, this may soon be replaced by complete cessation in contraction. Sodium salts are also probably essential to the heart apart from their function of maintaining a normal osmotic pressure in the fluid, for if the osmotic pressure be maintained by the addition of cane sugar, and the concentration of sodium be lowered to 0.2 per cent or less, the mammalian heart will cease to beat, though it recovers on the addition of sodium. Calcium is also essential to normal activity. In the absence of calcium the beats become smaller and the heart eventually stops in relaxation, as it does in the presence of an excess of potassium. If calcium is in excess relative to potassium, to which it acts antagonistically, the beat also becomes smaller but ceases through an incapacity of the heart to relax. It was originally shown by Mines[240] and has been confirmed by Baetjer and McDonald[17] that in the absence of calcium rhythmical electrical changes may be recorded when no mechanical contraction is demonstrable. The effect on cardiac frequency is complex; excess of potassium causes a slower beat, excess of calcium an initial increase followed by a decrease in rate. In other words, an optimal Ca/K ratio exists at which the frequency of the beat is highest, and an increase or decrease of this ratio slows the rhythm; the ratio of these ions in Ringer's solution is somewhat below this optimal value.

Hydrogen ion concentration also has a profound effect on cardiac activity, and may be concerned in the development of the primary stimulus. According to Andrus and Carter,[9] the frequency of the contraction of the rabbit's auricle is reduced if the pH of the perfusing solutions is lowered, and vice versa. Alkaline solutions favor stimulation. They advance the theory that the stimulus may depend on the potential difference between the inside and outside of the cells caused by differences in pH, and that the other ions affect the magnitude of this potential difference by altering the permeability of the membrane. The rhythm is thus due to "a rhythmic accumulation and discharge of a potential difference across a semipermeable membrane." There is still doubt, however, as to which are the primary ions concerned, and it is even uncertain whether the ions of Ringer's solution are really essential. Robertson[262, 263] claimed that the characteristic properties of Ringer's solution depend on a normal osmotic pressure coupled with a normal relation between the average diffusion rates of cations and anions. Such theories are difficult to establish, for, though the external environment may be altered, salts are still present in the muscle in considerable quantities and no real exclusion of the presence of any of the three cations is readily attained.

Various combinations of the main salts may be used in the so-called Ringer's solution and its modifications. Some recommended formulas are indicated in Table XIII. The solutions do not keep well when mixed; it is best to make up the glucose and bicarbonate solutions separately, to use concentrated stock solutions and to mix just before use.

TABLE XIII

SALT SOLUTIONS (AFTER SOLLMAN)

Percentages of salts (anhydrous)

Author	Adapted to:	NaCl	KCl	$CaCl_2$	$NaHCO_3$	Other Constituents
Ringer	Frog	0.6	0.0075	0.01	0.01	
Howell	Frog	0.7	0.03	0.026	0.003	
Locke	Mammals	0.92	0.042	0.018	0.015	Dextrose 0.1
Tyrode	Mammals	0.8	0.02	0.01	0.1	$MgCl_2$ 0.01 NaH_2PO_4 0.005 Dextrose 0.1

Site of Origin of the Beat: The Pacemaker

It has been pointed out that in vertebrate hearts with a slow beat the contraction wave may be seen to originate in the sinus venosus. Evidence that in the mammalian heart it originates in a corresponding area; namely, the sino-auricular node, is supplied by the following facts: (1) Warming or cooling the node increases or decreases, respectively, the frequency of the normal heart-beat, but has no such effect if applied to other parts of the heart. (2) Injury to the node may alter the frequency. (3) The rhythmic capacity of strips cut from the auricles is greater than that of other areas and is greatest in those cut from the region of the node. (4) Electrical records demonstrate that the initial galvanometric negativity commences in the node.

The last point may be considered in more detail. Any excitable tissue when activated develops an electrical potential (probably due to changes in a polarized surface layer) such that the active area is negative to one that is inactive. The negativity spreads gradually and is contemporaneous with, if not the cause of, excitation. If an excitation spreads along a muscle fiber, first one end becomes negative then, if the fibers are relatively short, both are negative; the negativity subsides first at the point originally active, and last at the more distant point. In this way a diphasic current is recorded by the galvanometer (see page 25). Electrical exploration of the auricle gives results which imply the spread of activation radially from a center at or near the sino-auricular node. If two electrodes be placed on the auricle, that nearer the origin of the impulse will develop a negativity first, that further removed later. It has been found also that if such contacts be made, and one be situated on the sino-auricular node, this contact develops negativity earlier than a contact on any other part of the auricle. Artificial electrical stimulation of the auricle can generate a contraction, and the electrical changes recorded then exactly duplicate those of a normal contraction only if the point stimulated is the sino-auricular node.

Other parts of the auricle show a capacity for initiating rhythmical activity, as do also the auriculo-ventricular node and, to a less extent, ventricular muscle, but the natural rhythm of the sino-auricular node is the fastest, and it consequently acts as a pacemaker. The spread of electrical changes from this center is able to "fire" consecutively the other parts of the heart. Since

the spread of the electrical changes provides the most valuable method of investigation of the propagation of the excitatory wave, the electrical changes that may be recorded in man by connecting a galvanometer with the periphery of the body must now be considered.

THE ELECTROCARDIOGRAM, OR E.C.G.*

The changes developed in both the auricle and the ventricle, create differences of potential and consequent currents in the saline mass constituting the body. The direction of spread somewhat resembles that which obtains when an isolated heart is immersed in a bath of saline, but is modified by the interference created by membranes such as the pericardium. The blood itself passing along the large vessels forms a ready conductor so that differences of potential exist at different parts of the body surface, and the action currents of the heart may be recorded by making contact with the body surface, preferably through the limbs. To obtain such contact the skin is moistened with saline and a (relatively) nonpolarizable electrode of silver foil (covered electrolytically with a layer of silver chloride) is held in contact with it. (More recently pastes of pumice and salt with appropriate nonpolarizable metallic electrodes have been introduced by the instrument companies; these give little trouble, and are coming into general use.)

The standard leads used are: I across the base of the heart by recording from the right and left arms; II along the long axis of the heart by recording from the right arm and left leg; and III along the left margin of the heart by recording from the left arm and leg. To these have now been added a precordial lead IV.

The various machines used to record the current need not be described in detail. Commonly they consist of some modification of the string galvanometer originally described by Einthoven. This consists simply of a powerful electromagnet between the poles of which is suspended a very fine wire or silver-coated quartz thread. To this thread the electrical contacts are wired, and any current passing through the thread causes it to move across the magnetic field. The thread is illuminated by a lamp and optical condenser, and its image is enlarged by a microscope and thrown onto a camera on which its movements appear as lateral movements of the string's shadow. By an appropriate horizontal cylindrical lens this vertical shadow is reduced to a spot which moves horizontally across the photographic paper. The paper in turn is moved vertically by a motor. In this way a graphic record of the potential changes is obtained, which (when turned through 90° for reading) shows time on the abscissa scale, and electrical potential in millivolts on the ordinates. Usually a rotating wheel is used to interrupt the light every 0.04 second so that time intervals of this duration are shown as vertical rulings on the records, while the cylindrical lens is ruled vertically with lines 1 mm. apart, so that these lines appear as horizontal lines on the record. In use, the string is standardized by adjusting its tightness, and consequent sensitivity, so that an E.M.F. of 3 millivolts gives an excursion of 3 cm. when put through the circuit of string and subject from the switch board. Then each millimeter of the vertical scale corresponds to an E.M.F. of 0.1 millivolt. In practice relatively high, more or less steady, potential differences occur between the two electrodes, dependent on variations in the sweat and salt concentrations of the skin of the two areas, or on corrosion of the electrodes or of the lead wires, etc.; these other potentials are usually neutralized by balancing against them opposite potentials derived from a dry cell and potentiometer. In other machines their effect may be obliterated by the inclusion of appropriate electrical condensers in the leads. Other methods of recording involve the use of oscillographs such as that described by Matthews, or a cathode-ray oscillograph (Fig. 25). These require previous amplification of the currents

*E. K. G. in German terminology.

but, if the amplification is free of distortion, values equivalent to those of the direct record may be obtained, or, with the Matthews or cathode-ray oscillograph, values with even greater accuracy and magnification.

Because of the complex anatomical relations of the muscle fibers to one another (see Figs. 109 and 110), not only in the connections of one chamber with another, but also within a single chamber, it is difficult to predict the form of the normal E.C.G. It is even more difficult to predict the deviations from the normal, which are associated with pathological changes. Through long years of clinical experience and experimental attack, it has gradually become possible to use the electrical variations as a valuable diagnostic tool.

The terminology of cardiac activity in common use requires explanation. Contraction in the heart is called *systole,* which may therefore be either auricular or ventricular, though if not otherwise specified, systole refers to ventricular contraction. *Diastole* is used to indicate the resting period between successive

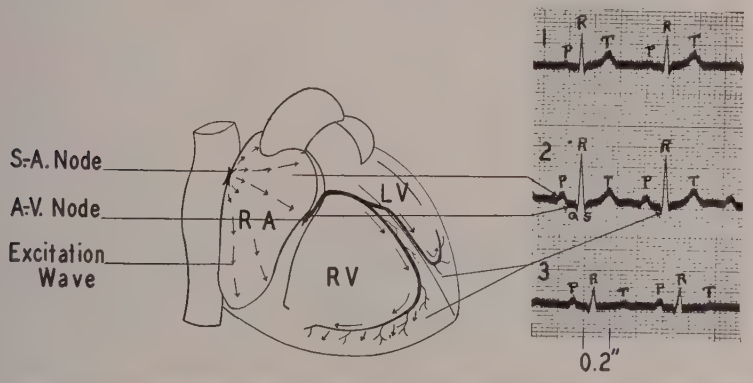


Fig. 106.—Electrocardiogram Leads I, II, and III, with diagram of the heart showing schematically the origin of the waves.

systoles. The adjectives corresponding with these periods are *systolic* and *diastolic,* and refer to events contemporaneous with systole or diastole, or generated by them. Systole refers to the mechanical contraction rather than to excitation, but the electrical changes that accompany systole are properly called systolic; they are often called, less accurately, electrical systole.

A *normal electrocardiogram* in man is shown in Fig. 106. In diastole, between waves lettered T and P (as well as in certain stages of systole) the string lies at its position of zero potential. From this zero it is moved upward or downward by waves lettered, and conventionally named, P, Q, R, S, and T. Of these P, R, and T are above the zero line (relative negativity of right arm over left arm or left leg in Leads I and II, of left arm over left leg in Lead III) while Q and S have the reverse polarity. The relation of these electrical changes to the mechanical events may be seen in Fig. 132. The durations of the waves are measured from the commencement of their divergence from the zero-potential line (see indications of duration of P and T in Fig. 132), i.e., the duration of the P-wave is measured from the start of its upstroke to the bottom of its downstroke. It will be observed (1) that the P-wave develops just antecedent

to the contraction of the auricles, as indicated by a rise in intra-auricular pressure, (2) that the increase in intraventricular pressure commences after the Q-wave, usually during the upstroke of the R-wave, and (3) that the T-wave ends at approximately the same time as ventricular contraction. Following T another low wave above the zero line may sometimes be seen. It is known as U and develops in the early part of diastole. Little is known of its causation. Records obtained in cases of heart block, where the auricular and ventricular contractions are dissociated, demonstrate that P is associated with auricular systole, Q, R, S, and T with ventricular systole. The waves Q to T represent the algebraic summation of the changes in the two ventricles, and those reproduced in Fig. 106 fall within the limit of normal curves. When the right ventricle is relatively large compared to the left (e.g., in mitral stenosis), there is a tendency for the R-wave to be small and the S-wave to be very large in Lead I, and for the R-wave to be very large and S very small or absent in Lead III. This is known as right preponderance. On the other hand, when the left ventricle is very large (e.g., in aortic regurgitation) the opposite condition is seen; in Lead I, R tends to be large and S small or absent and in Lead III, R to be small and S very large. This is known as left preponderance.

Propagation of Excitation in the Auricles.—The origin of the impulse in the sino-auricular node has already been discussed. From this place of origin the spread of the excitatory wave through the auricle may be followed by the development of electrical negativity; according to Lewis[215] the spread is at a rate of about 1 meter a second. No special conducting tissue appears to be present, though the transmission is thought to follow certain direct muscular fasciculi.[110] Auricular activity is indicated by the P-wave, which is generated by the gradual spread of activity to the whole of the auricular walls. The electrical changes associated with activity probably last throughout auricular systole and are comparable to those observed in the ventricle (to be discussed later). The return of the galvanometer to the zero potential line at the end of P does not then imply a cessation of these electrical changes, but rather that they have at this point developed throughout the auricles. Developing at different times at different places the electrical changes also subside unevenly, and create another wave similar to the T-wave formed in the ventricle, but this wave is of too low a potential to be obvious in the ordinary electrocardiogram, though it may be demonstrated in the isolated auricle.[240]

Propagation of Excitation From Auricle to Ventricle.—The auricular excitation spreads to the auriculo-ventricular node, which is reached earlier than are some of the more distant areas of the auricles. The impulse reaches the node a little after the attainment of the peak of the P-wave. The spread through the auriculo-ventricular node is slow, so that there is a considerable delay (0.05 to 0.10 sec.) in transmission in this area which makes the total duration of conduction from the pacemaker to the ventricle 0.12 to 0.18 or even 0.20 second. This interval, measured from the start of the P-wave to the beginning of the ventricular electrical complex (whether Q or R), is known as the P-R interval. Values above 0.20 second usually imply impaired conduction.

Propagation of Excitation in the Ventricle.—The spread of excitation from the auriculo-ventricular node to the ventricle occurs along the auriculo-ventricular bundle of His. The electrical changes generated within this bundle are not de-

tectable in the E.C.G., but the gradual spread of activity through the powerful ventricular muscle, which is thereby induced, gives rise to the complex series of waves comprising the QRS group. This normally lasts about 0.08 second, but may slightly exceed 0.1 second when the heart is abnormally large and the distance for conduction thereby increased. It may considerably exceed this value when conduction in the branches of the bundle of His is impaired, so that part of the conduction is through muscular channels. When all the ventricular muscle has been rendered active, electrical changes continue, but are balanced and the galvanometer returns to the zero-potential level in the S-T interval. The uneven subsidence of activity creates the T-wave,[192] the disappearance of which indicates the final end of all detectable excitation. That the T-wave is indeed dependent on uneven subsidence of activity was demonstrated strikingly in Mines' experiments[240] on the frog's heart. In the frog the negativity commences at the base, spreads to the apex, and returns again to muscle near the base, so that the T-wave is positive (base negative to apex) as it is in Lead II in man. If now

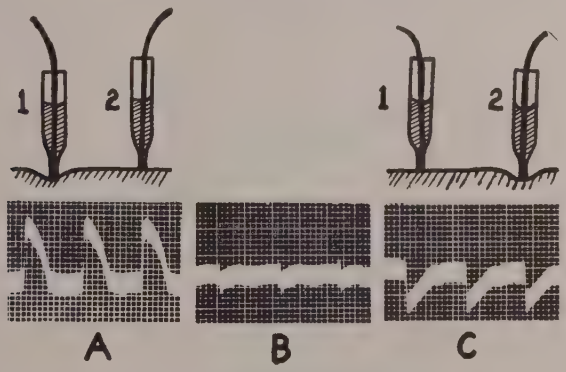


Fig. 107.—Curves demonstrating reversible monophasic electrical effects. *A*, moderate pressure at electrode *1* preventing functioning of tissue under this electrode and giving monophasic curves; *B*, normal record with light pressure on electrode *1* and heavy pressure applied to electrode *2*; *C*, record obtained as in *B*, but three seconds later when tissue under *2* had been affected by the pressure. (From Jochim, Katz and Mayne: Am. J. Physiol. **111**: 177, 1935.)

the apex of the heart is cooled, so that activity at this point is unduly prolonged, the T-wave becomes negative (negativity at the apex outlasting that at the base); when the apex is allowed to warm, the T-wave returns to its usual condition of positivity.

Further indication that the ventricular complex (Q, R, S, and T) is dependent on the irregular balancing of numerous relatively simple plateau-like electrical changes is indicated by the recording of the changes developed in a single unit. These are not readily recorded but may be shown by differences. An ingenious method of producing temporary local failure of the active change at a point in the muscle was adopted by Katz and his associates.[188] It depends on the production of a local anemia by pressure applied to the surface. The local failure at one electrode allows the unbalanced monophasic potential developed in the region of the other electrode on normal tissue to be demonstrated (Fig. 107). The primary potential is indicated as a plateau-like negativity

developing at or slightly before the contraction wave and lasting throughout contraction. This long duration, contemporaneous with contraction, is in striking contrast with the conditions in skeletal muscle, and is apparently associated with the long absolutely refractory period observed in cardiac muscle (see page 344) and with the consequent incapacity of the muscle to develop tetanus. For discussion of the fundamental character and origin of the electrical changes the papers of Craib,[78] Wilson,[319] and of Goldberg and Eyster[140] may be consulted.

Rate of Spread of Excitation to the Ventricle.—This was investigated by Lewis[215] by the method of taking direct leads from the ventricle of a dog and comparing the onset of negativity with the time of the upstroke of the R-wave in Lead II. In such a way data were obtained, some of which are represented in Fig. 108. Histological examination showed that the branches of the auriculo-ventricular bundle were shortest and came relatively close to the surface where the times were shortest. On these grounds he concluded that conduction through the A-V bundle is relatively rapid (4 meters a second) and much slower (0.4 meters a second) through the muscle itself. He assumed, however, that on reaching the muscle the impulse

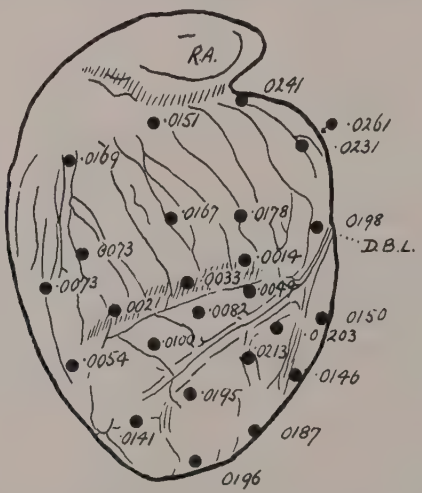


Fig. 108.—Diagram of experiment by Lewis showing the times at which the excitation wave appeared on the front of the heart relative to the upstroke of *R* in Lead II. *R.A.*, right appendix; *D.B.L.*, descending branch of left coronary artery. (From Thomas Lewis.)

travels from the endocardial to the pericardial surface by the shortest possible path, without regard to the arrangement of the muscular fibers. This part of his hypothesis is certainly *a priori* improbable, and has been criticised both on theoretical and on experimental grounds by Sands Robb.[261] It seems more probable that the actual transmission is along the muscle fibers from their point of contact with the A-V bundle, and on this basis a velocity of transmission in the muscle fibers of 2.4 meters a second is found.

The general structure of the superficial bulbospiral and sinospiral muscles is shown in Figs. 109 and 110. Above them are shown the electrocardiographic changes observed in the 3 leads when these muscles are injured. It has been found by Robb and her associates that once damage has been produced in one of these muscle bands, and the characteristic change in the E.C.G. has resulted, no further alteration is produced by additional damage to the muscle in another area. This implies that the sole effective stimulation of the fibers proceeds from the A-V bundle by transmission along the muscle bands, or along finer branches of the bundle which follow these bands. That fine arborizations of the bundle exist has been demonstrated by Abramson and his collaborators.[1, 63]

The Electrical Axis.—The electrical changes accompanying heart activity have been explained as the effects resulting from the sum of numerous electrical changes which develop in different areas, spread in different directions, and which may summate with, or neutralize, each other. The resultant electrical potential represents a force of a certain magnitude and direction in the three dimensions of space. The presence of this force may be demonstrated in the electrocardiogram by the use of four leads. Of these the three standard leads (I, II, and III) deal with the two dimensions of the frontal plane, while the fourth lead (IV) is used to obtain an indication of the spread anteroposteriorly. The true electrical axis, which indicates orientation in space of the sum of the electrical potentials, should theoretically be expressed in the three dimensions of space. For simplicity the frontal plane represented in the two dimensions of the three standard leads is alone considered. The term "electrical axis" consequently represents the orientation in this frontal plane.

Fig. 109.—Superficial bulbospiral muscle, posterior view. *M* represents the mitral valve and *T* the tricuspid valve; *A* the aorta; *L* is the left and *R* the right ventricle; *P* and *P P M* are papillary muscles. Characteristic changes in the three leads of the E. C. G. following injury to this muscle are shown above; they are depression of R-T in Lead I, elevation in Leads II and III. (From Robb, Hiss and Robb; Am. Heart J. **10**: 289, 1935.)

The heart lies within the chest surrounded by blood-containing tissues of relatively high electrical conductivity. An electrical field is set up in the body by the cardiac potentials, and currents circulate through the tissues. The conduction is mainly through the blood present in the larger vessels. Spread of current occurs also through other tissues, but this is not distributed regularly owing to the effects of membranes, such as that of the pericardium (Katz[194]). With modern methods of electrical recording after amplification it is common to find cardiac potentials appearing as artifacts during attempts to obtain records of nerve or muscle potentials in almost any part of the body. The two arms with their large entering vessels form convenient leads for withdrawing current from the right and left upper poles of the electrical field. If the two arms be joined by wires which pass through a galvanometer, this outer circuit forms an alternative path through which current may flow to activate the galvanometer. The electrical potentials so determined, as well as the current flowing through

the external circuit, represent but small fractions of the actual potentials developed in the heart and of the total flow of current. In a similar way the legs (in practice the left leg is normally used) provide leads through which current may be withdrawn from the lowermost pole (pubic area) of the electrical field. The points from which the cardiac currents may be thus "tapped" may be considered as the three angles of an equilateral triangle, represented in Fig. 111, *A*, with the points of the leads through the right and left arms and left leg labelled respectively R, L, and F.

Let us assume that the actual potentials of the heart summate and that their sum may be represented as a potential oriented in the frontal plane by the line originating in O (Fig. 111, *A*) and of a magnitude which may be represented graphically by the length of this line. This line then represents the electrical axis at the time under consideration; and its length indicates the maximal potential, which could be "tapped" in the frontal plane. This is designated the *manifest potential*. The actual potential developed is likely to be larger.

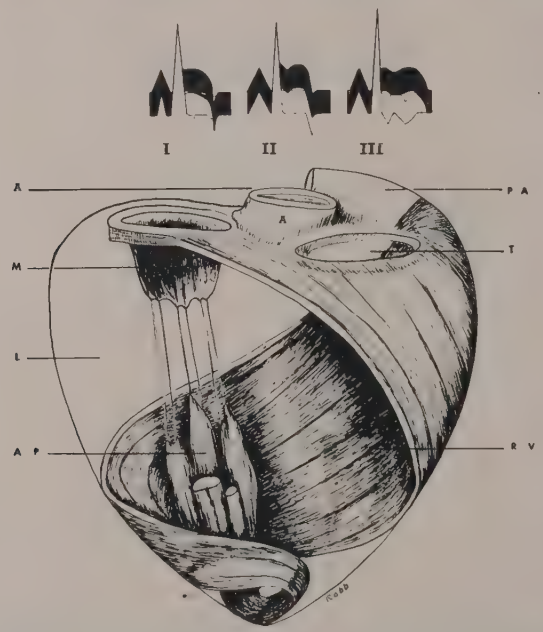


Fig. 110.—Superficial sinospiral muscle, posterior view. The lettering is the same as in Fig. 109, except *R V* is the right ventricle and *A P* represents papillary muscles. *P A* is the pulmonary artery. Characteristic changes in E. C. G. with injury are slight elevation of R-T in all leads. (From Robb, Hiss, and Robb: Am. Heart J. **10**: 289, 1935.)

The manifest potential would equal the actual potential only if the latter were developed exactly in the frontal plane and had no anteroposterior component. (If the actual potential could be developed exactly in the anteroposterior plane, the manifest potential in the frontal plane at right angles to it would obviously be zero.) The *derived potentials* that may be "tapped" and recorded by the three leads may then be represented by the projections of the line representing the manifest potential onto the three sides of the triangle. This relationship depends on geometrical principles, and implies that the potential recorded in Lead II is always equal to the algebraic sum of the potentials recorded in Leads I and III. In spite of the complexities introduced by the actual position of the heart within the chest and the pericardial sac, this relationship actually obtains except for relatively small discrepancies. It may be seen to be approximately true in Fig. 106. Here exact comparison is impossible

since the records were not obtained simultaneously and the peak of the R-wave (or any other reference point) in one lead may not be contemporaneous with that in another. For accurate comparison the measurements must be made at exactly comparable times. This is achieved by using two galvanometers recording simultaneously (or a two-stringed instrument). Lead II is recorded throughout, and the potentials of Leads I and III are read at times determined by reference to Lead II. It is clear that the procedure just described may be reversed and the magnitude and direction of the manifest potential may be calculated from the potentials recorded from any two leads, *if these leads be recorded simultaneously.*

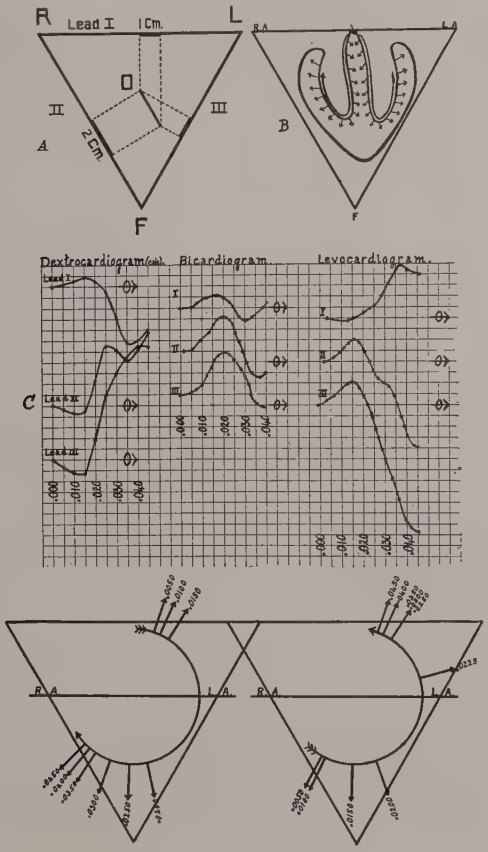


Fig. 111.—*A.* Schema to illustrate method of determining the electrical axis, and to show its projection on to the three leads.

B. Diagram showing direction of spread of excitation wave in the heart, and the relations of electrical axis to the three leads at different instants. (Modified from Lewis.)

C. Curves illustrating the composite nature of the physiological electrocardiogram. The two curves on the right were charted from the electrocardiograms of a monkey before and after the right conducting branch had been compressed. The dextrocardiogram was subsequently calculated from these curves. Ordinates, 0.2 millivolts. Abscissae, 0.005 sec. (Modified from Lewis, Tr. Roy. Soc., 1916, ccvii.) Below, diagrams have been constructed from data published by Lewis, showing rotation of the electrical axis in each chamber during the production of the respective curves. The embracing triangle will conveniently serve to show the relation of the axis to the three leads. Compare this relationship with the changes in potential, plotted above.

For instance in Fig. 111, *A*, let a line be laid off along the line R L from its center to a length equivalent to the E. M. F. recorded in Lead I (in the figure this line is represented as 1 cm. in length from the center of the line R L and extends to the right to represent an upward deflection). Let a line be laid along R F also from its center to represent the E. M. F. recorded simultaneously in Lead II (in the figure this line is represented as 2 cm. in length). Lines drawn at right angles to the sides from their centers will meet at the center of the triangle (point O). Lines drawn from the other ends of the lines also at right angles to the sides will meet at some other point either within, or without, the triangle. The line joining

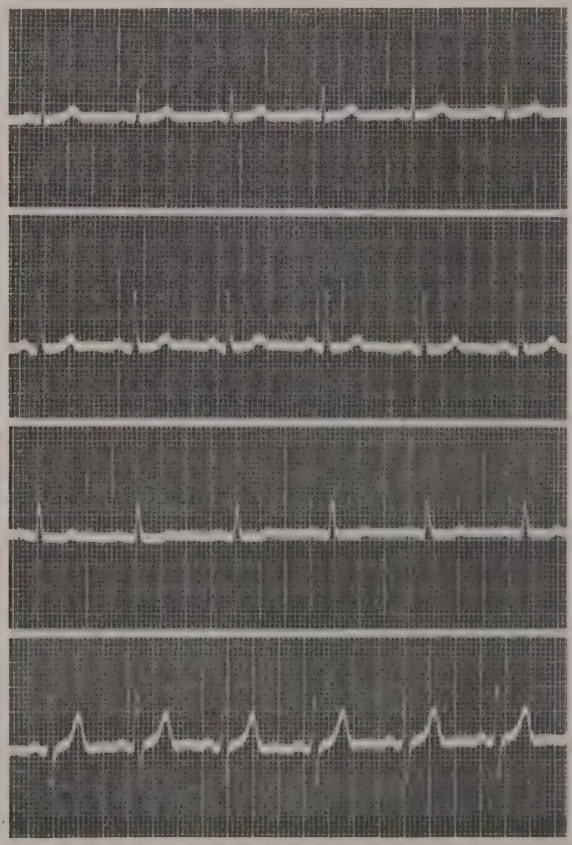


Fig. 112.—Records from a normal subject taken with Leads I, II, III, and IV R. (Courtesy of Dr. L. B. Laplace.)

this point of intersection to O represents by its direction the electrical axis and by its length the magnitude of the manifest potential. The electrical axis is not constant throughout the cardiac cycle; its direction is, on the contrary, constantly changing.

The electrical changes may be considered as the resultant of two separate changes, one due to spread of activation in the left ventricle, the levocardiogram, and the other to spread in the right, the dextrocardiogram. The algebraic sum of the two is the ventricular electrocardiogram or bicardiogram. The spread of activation into the two ventricles is represented diagrammatically in Fig. 111, *B*. The earlier stages of the ventricular complexes (QRS group)

obtained in a monkey are shown in Fig. 111, *C*. The bicardiogram is in the center. The levocardiogram, shown at the right, was obtained after conduction along the right branch of the A-V bundle had been prevented by compression. The dextrocardiogram was then derived from the difference between these two recorded sets of curves. From these potentials the direction of the electrical axis has been calculated, and is shown in the triangles below. Thus in the levocardiogram, 0.020 second after the start of ventricular activation, the E. M. F. is approximately 0.1 M V in Lead I and 0.2 M V in Lead II. The conditions might therefore approximately be represented by the lines shown in Fig. 111, *A*, and the electrical axis by the line originating from O. The direction more exactly determined in the original records is shown below by the line and arrow labelled 0.020. The circular line transverse to it represents the alteration of the electrical axis with time as the impulse spreads through the left ventricle. This line at right angles to the electrical axis is at any moment clearly related to the spread of excitation through the main left branch of the A-V bundle (compare it with the left ventricular conduction indicated in Fig. 111, *B*).

The principle underlying the determination of the electrical axis was developed by Einthoven, and the triangle is consequently known as Einthoven's triangle. It was used by him and others to analyze the principles of electrical transmission of activity. In this field it has proved of great value; it is not much used in clinical electrocardiography. The variation of the types of the electrical changes recorded in the three leads with the relative sizes of the ventricles and the identification of these variations as those associated with right or left ventricular preponderance have already been described (p. 352). Actually the differences noted depend on the alterations produced in the electrical axis. They may consequently be encountered if the position of the heart is altered without any change in the relative sizes of the ventricles; they may, therefore, develop in a condition of pneumothorax when the heart is displaced by abnormal pressure changes in the pleural cavities. The change in balance with hypertrophy need not depend on imbalance due to the abnormally large mass of one ventricle; it may depend on the longer time taken for conduction of activation throughout the larger ventricle.

Precordial Leads—Lead IV.—Following the studies of Wolferth and Wood[323] the use of anteroposterior leads has come into general clinical use. The technique approved by the American Heart Association and the Cardiac Society of Great Britain and Ireland is to move the electrode from the left leg to the precordium. The indifferent electrode may be the electrode on either arm or an electrode on the leg or on the back in the region of the scapula. The records thus obtained resemble in shape those of standard leads, but the upstroke represents positivity, not negativity, of the active precordial electrode. In the records in the older literature the direction of lead was the opposite of this, and the records had opposite polarity. In the newer nomenclature the various modifications of the precordial lead are labelled according to the position of the indifferent electrode, thus IV R is used to indicate an indifferent electrode on the right arm, IV F, on the foot, and IV B on the back. A record obtained in a normal subject with the first of these (IV R) is shown at the bottom of Fig. 112.

ABNORMALITIES OF CONDUCTION AND EXCITATION

Auriculo-Ventricular Conduction and Heart Block.—The rate of conduction of the impulse from the auricle to ventricle determines the time interval between the auricular and ventricular contractions, and this interval is, therefore, of the same order as that which separates the electrical changes. In the human heart the normal A-V interval is 0.12 to 0.18 second. Durations which exceed 0.20 are almost certainly abnormal, except when they are associated with a very slow pulse rate. Excessively slow conduction usually implies conduction by damaged tissue. This may be demonstrated experimentally by ap-

plying pressure to the auriculo-ventricular connecting tissue in the frog or turtle heart by means of an adjustable clamp (Gaskell clamp). When the pressure is light, the conduction time is long; as the pressure is increased the time is further lengthened until ultimately partial block occurs. Under these conditions two impulses may be conducted, the second more slowly than the first, and then fatigue in the damaged tissue may so lengthen its refractory period that conduction fails completely for the third beat; the resultant rest allows recovery so that two more impulses are carried and so on. With greater pressure the auriculo-ventricular ratio may become 2 to 1 or 3 to 1 or some higher ratio, and eventually complete dissociation of the two chambers may develop. Then each chamber beats at its own independent rhythm.

Clinical conditions of this type are frequently encountered and it will be instructive to consider some of them.

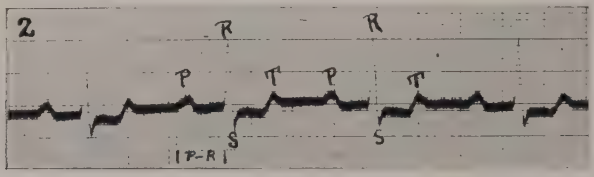


Fig. 113.—Delayed conduction. Note the normal appearance of the electrocardiogram except for the prolongation of the *P-R* interval, which measures 0.23 second.

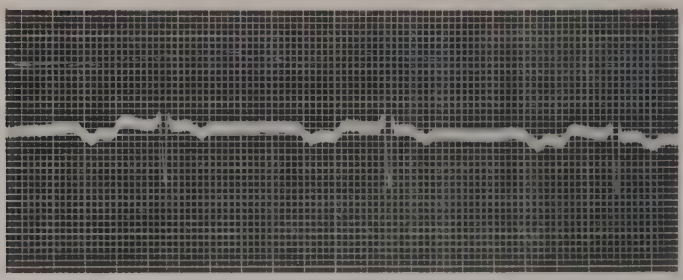


Fig. 114.—A record from Lead II in a subject with an auricular rate of 84 and a ventricular rate of 42. The auricular P-waves may be recognized by the fact that in this subject they happen to be double. One such double wave precedes each ventricular complex by the somewhat lengthened PR-interval of 0.24 sec. Another auricular wave fuses with the end of each ventricular T-wave and induces no excitation of the ventricle. (Courtesy of Dr. L. B. Laplace.)

Auriculo-Ventricular Block.—The most common site of impaired conduction is in the A-V node and bundle of His. Slight damage to this tissue is indicated merely by an abnormally slow rate of conduction. The P-R interval is consequently lengthened beyond 0.20 second (Fig. 113). With greater damage conduction may fail altogether, giving "complete block," or an intermediate stage of "partial block" may develop. In partial block a single ventricular beat may be missed in 5 or 6 pulses or 3 out of 4 impulses, or even more, may fail to be conducted. Any other intermediate ratio may be found. In man, as in the turtle, there is some recovery of conduction following the impulse which fails to be conducted. The longer interval gives an improved recovery. Following the missed beat the P-R interval may be almost normal

in duration. With each following beat, that is conducted, recovery is incomplete, so that successive beats cause accumulated fatigue with a progressive lengthening of the P-R interval until conduction again fails. The effects of changes in the rate of auricular contraction or in conduction to the ventricle are illustrated in Figs. 129 and 130 (page 371) where heart block is demonstrated in simultaneous mechanical records of auricle and ventricle. A heart block in man demonstrated by the electrocardiogram is shown in Fig. 114. It represents a 2 to 1 rhythm, the simplest type of partial block.

Other factors besides fatigue may impair conduction and exaggerate the effects of damage. Among these an inadequate supply of oxygen (anoxemia), toxic conditions such as occur in fever, and reflex vascular changes associated with increased vagal inhibition of the heart are important. Conditions associated with a blood pressure rise, including the after-effects of a heavy meal, may result through reflex vagal effects in the exaggeration of simple slowed conduction rate into heart block.

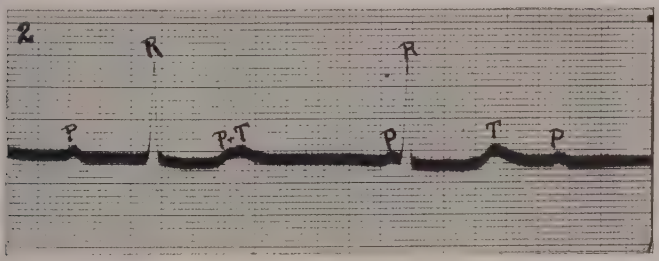


Fig. 115.—Complete dissociation. Note that the P-wave occurs regularly and bears no definite relation to the R-wave of the ventricular complex. Auricular rate 72. Ventricular rate 40.

In complete heart block the rhythms of the auricles and ventricles are completely independent and the P-wave may occur anywhere in the ventricular cycle (Fig. 115). The P-waves like those of the ventricle continue to maintain a definite and regular rhythm. In the presence of complete heart block the pulse rate is usually of the order of 30 to 40 per minute, and this ventricular rate can be modified only slightly by the subject. Slight changes are probably produced through the accelerator nerves which, unlike the vagus, have some direct connections with the ventricle, or they may result from liberation of adrenalin.[88]

Bundle-Branch Block.—Another form of block is due to impaired conduction which is limited to, or more marked in, one of the branches of the A-V bundle. Under such conditions conduction in part of the ventricular system is initiated more or less normally, but in the rest only after a considerable delay. Usually one of the main branches, right or left, is involved, and then presumably the whole of one ventricle starts to contract earlier than the other. The latter is put into activity either by conduction along the various muscle bands which are common to the two ventricles, or through the finer branches of the A-V bundle, or through the direct connections of the muscle fibers. It is certain that both ventricles can contract when one branch of the bundle is completely divided. That the contraction on the side in which the bundle is damaged is delayed and that consequently the electrical changes recorded are not normally balanced are equally certain. The type of the electrical changes which accompany lesions of the right branch as distinct from those of the left is still controversial. The effects of division of one or the other bundle-branch were in-

vestigated in the dog[215] and the conclusion drawn that left ventricular complexes are associated with a marked upward deflection (R) in Lead I and a marked downward displacement (S) in Lead III. On the assumption that the initial deflections represent the effect of the unbalanced ventricle with normal conduction, the records shown in Fig. 117 would be classed as caused by block of the left branch, those in Fig. 116 as the result of block of the right branch. It has already been shown that the electrical changes recorded depend on the electrical axis, and vary, therefore, with the position of the heart. It is uncertain whether the orthodox view can be extended to apply to the human heart. Evidence that the type of curve shown in Fig. 117 is due to damage of the right bundle-branch and, therefore, is the result of the earlier contraction of the left ventricle has been advanced by many.[318]

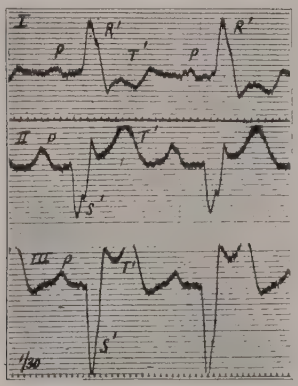


Fig. 116.

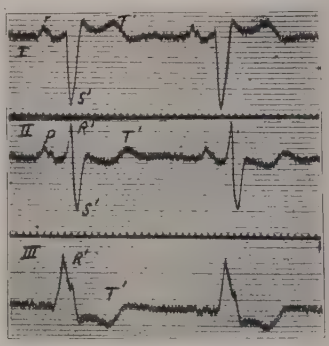


Fig. 117.

Fig. 116.—Electrocardiogram showing a lesion of the right branch of the conducting bundle. Note that the *T*-wave in this curve and in the succeeding one is opposite in direction to that of the chief deflection (*R* or *S*) in the initial phase, and that the *QRS* complex is prolonged. (From Carter.)

Fig. 117.—Illustrating the effect upon the electrocardiogram of a defect of the left division of the bundle. (From Carter.) In the modern terminology the designation of right and left bundle-branch block has been reversed. According to the present style, in the above figures "right" should read "left" and "left," "right."

Fibrillation and Allied Conditions

Abnormalities of conduction and excitation may so interfere with the spread of excitation to all the fibers of the heart that the all-or-none behavior is no longer in evidence. Conditions known as pulsus alternans, auricular flutter and fibrillation and ventricular fibrillation probably all originate in this way. Such breakdowns may be produced experimentally, or appear clinically as the result of pathological changes. They throw considerable light on the mechanisms normally at work. Under normal conditions the excitatory state is conducted relatively rapidly over the heart and induces activity in its various parts in rapid succession. Contraction is associated with the development of a refractory period of long duration, and the presence of this refractory state prevents the return spread of activation from the area last excited back to the area from which the excitation originated. A coordinated rhythm, with pauses for relaxation and filling between contractions, is thus ensured. If the *refractory period is abnormally lengthened* in some fibers as the result of damage, these fibers may not respond to every impulse, and alternating powerful and weak contractions (pulsus alternans) may be seen. Another possibility is that the contractions of some or all of the fibers may be weak, of short duration,

and associated with an *abnormally shortened refractory period.* If this condition be accompanied by a slow conduction rate, the activation of the most distant area may spread back to the areas activated earlier. This is called *re-entry,* and the condition may lead to a circular spread of reactivation from one area to another in what is termed a *circus movement.* Such conditions may cause what is known as flutter and fibrillation. In the latter the all-or-none law is completely abrogated.

Pulsus Alternans.—In clinical cases a condition may occur in which the pulse is alternately strong and weak, and in which the alternation has no relation to respiratory rhythms. Electrical records sometimes show no differences between the two pulses; more commonly the complexes are similar but the potentials developed during the beats which give the smaller pulsations are slightly greater. This probably indicates that the whole of the ventricular wall does not contract at each systole but that part of the muscle is damaged, has a long refractory period, and responds only to every other beat. The larger electrical change is then an indication of an abnormal electrical balance. That this explanation is probably correct is indicated by the common occurrence of such responses in excised cold-blooded hearts when they are in poor condition. It is also indicated by the experimental method used by Mines.[241] He used a ring of auricular muscle from a turtle (Fig. 118, *A*) in which the thread tied at the apex so constricted the muscle as to prevent conduction. The

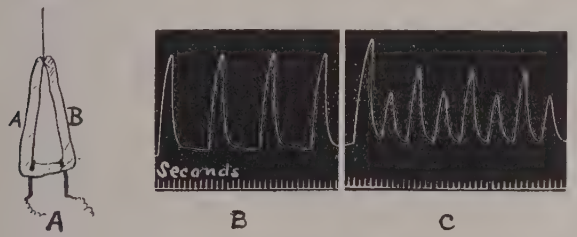


Fig. 118.

Fig. 119.

Fig. 118.—*A,* ring of tortoise heart with stimulating electrodes shown; the ligature at the apex blocks conduction at that point. *B,* response of both sides to every other stimulus. *C,* alternating responses of the two halves of the ring, each half reacting to every other stimulus. For discussion see text. (From Mines: J. Physiol. **46**: 349, 1913.)

Fig. 119.—Diagram of a ring made from a tortoise heart. This preparation is capable of developing circus movements. (From Mines: J. Physiol. **46**: 349, 1913.)

ring was stimulated electrically and both sides contracted together. Then the rate of stimulation was increased until the ring responded only to every second stimulus when a record of the type shown in Fig. 118, *B* was obtained. If now a mechanical stimulus was applied to one side just before the electrical stimulus arrived, this side reacted to the mechanical stimulus and so became refractory to the electrical stimulus. As a result the two sides of the ring responded to alternate stimuli, instead of together. The response was then that shown in Fig. 118, *C* which is of the pulsus alternans type. In clinical conditions it is more probable that one section of the muscle responds to every stimulus, another only to every second stimulus.

Auricular Flutter.—It was shown by Mayer in 1906 that an excitation wave may be made to travel continuously in a circular manner around the bell of a jellyfish. In 1913 Mines[241] and Garrey[135] independently showed that the same phenomenon may occur in heart muscle. Mines performed his classic experiment with a ring of tortoise heart arranged as indicated in Fig. 119. The ring consists of both auricular and ventricular tissue, and conduction from one to the other is slow. At each end of the ring, at the apex of the ventricle and in the auricles, muscle is cut away to leave only a small bridge of conducting but damaged tissue. Conduction is, therefore, slowed also at these points. If the heart is stimulated, impulses are transmitted in both directions, and the waves meet at the opposite end of the ring where each is extinguished by the refractory state set up by the other. If repetitive stimulation is used, a second stimulus may find the tissue on one side of the ring still refrac-

tory and fail to initiate an excitation, while it is just successful in doing so on the other side. The impulse set up, meeting no other wave, is not extinguished, but passes around the circle to its original starting point. Because the damaged tissue conducts slowly and the feeble contraction has a short refractory period, the wave finds the original point of stimulation no longer refractory, and the excitation once started can proceed more or less indefinitely. This is called a circus movement; it maintains a wave of contraction in tissue previously showing no spontaneous activity. It is not a true rhythm, for if another stimulus is given to the quiescent part of the ring, excitation travels in the opposite direction and meets the circus excitation, whereupon both waves are extinguished and the entire tissue becomes quiescent.

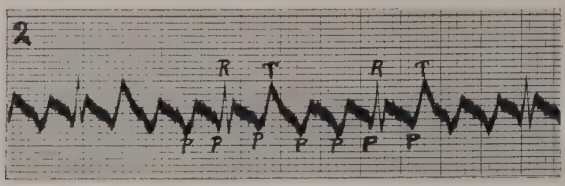


Fig. 120.—Auricular flutter. Auricular rate 300. Ventricular rate 80. Note the inversion of the *P* deflections.

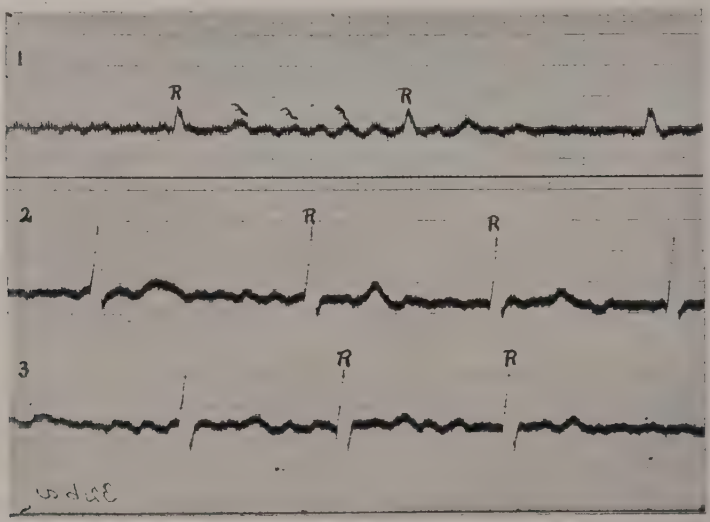


Fig. 121.—Auricular fibrillation. Leads I, II, and III. Note the coarse fibrillation waves between the *R* peaks, and the absence of any *P* deflections in relation to *R*. Note also the unequal spacing of the *R* deflections.

The behavior of this ring of cardiac tissue was immediately used by Mines to explain the origin of the rapid auricular contractions of the mammalian heart known as flutter and fibrillation, but his theory was attacked on its presentation to the English Physiological Society, particularly by Lewis, who afterwards became its chief proponent.

The essential elements for the development of circus excitation and movement are a *slow conduction rate and a short refractory period.* This combination of changes is capable of breaking down the normal simultaneous contraction of all the fibers of the heart muscle. Circus excitation cannot be maintained if the ring is so short that the duration of the refractory period exceeds that of the conduction. Consequently it may be broken if the conduction rate is improved, or if the refractory period is lengthened.

In auricular flutter the auricle beats regularly at a rate of 230 to 350 per minute. Such a rate is too rapid for the A-V bundle and the ventricle to follow, and a partial block is set up in which the ventricle may respond regularly or irregularly to some of these impulses (Fig. 120). The P-waves are large and abnormal in form but quite regular. Lewis[215] has investigated the responses of the auricle of the dog's heart to stimuli at 300 or more per minute. The auricle beats rapidly and, when the impulses are withdrawn, may continue this rapid rhythm. Lewis concluded that a circus excitation passes over a definite path in the auricle and radiating paths of excitation proceeding from it stimulate the rest of the auricle. While it is difficult to prove absolutely the presence of such a circus excitation, certain experimental facts indicate that it may be the cause of flutter and certain related conditions. Lewis found that when the auricle is made to beat at a high rate, its refractory period is reduced to 0.12 sec. or less, and its conduction rate slowed to half its normal value; the conditions are obviously favorable for the setting up of a circus wave. The circus movement is believed to follow an irregular ring having a diameter of some 3 or 4 cm. and situated around the orifices of the large veins. Some have considered the circus excitation theory unestablished, and have explained the phenomenon of flutter on the basis of a short refractory period in some abnormal ectopic focus. At present the circus movement theory is for the most part accepted, and seems more likely to be extended to explain other phenomena than to be denied. Garrey[135] expresses the opinion that it is the mechanism concerned in the production of tachycardia, flutter, fibrillation, and some types of extrasystoles.

Auricular Fibrillation.—This condition resembles auricular flutter from which it may develop. In it the auricular contractions are irregular and incoordinated. On the basis of the hypothesis that the phenomenon is due to circus excitation, the movement seems to be over rings about ½ the diameter of that in flutter; the wave recurs about 400 to 600 times a minute, but the path of the movement is not constant. To these waves of excitation the A-V node and the ventricle respond irregularly, so that the ventricles show perpetual arrhythmia (Fig. 121).

The treatment of auricular fibrillation by drugs is based on attempts to change the speed of conduction and the length of the refractory period. A drug which lengthens the refractory period while speeding conduction would be ideal. Those now used lengthen the refractory period but also slow conduction; they may, however, by exerting a relatively greater effect on the refractory period than on conduction rate, prove effective.

Ventricular Fibrillation.—This resembles auricular fibrillation but occurs in the ventricles, and, if fully developed, stops all blood flow including that in the coronaries. It is then fatal. In cats spontaneous recovery from experimentally produced ventricular fibrillation may take place, but recovery from fully developed fibrillation is very rare in most of the larger mammals. The condition can be induced by an electric shock. It may also result from deficient blood supply through failure of the coronary circulation. Adrenalin may be a cause under certain circumstances. This substance causes hyperexcitability of the ventricular muscle and when injected intravenously or liberated by prolonged splanchnic stimulation in an animal under anesthesia of a certain type (e.g., chloralose) it may cause paroxysmal ventricular extrasystoles; under conditions of high blood pressure these may give rise to very aberrant electrical complexes with very feeble mechanical contractions. The changes fall short of fibrillation, and the heart may recover. An example of this effect is the action which adrenalin tends to have in the early stages of chloroform anesthesia. Here the heart is slowed by hyperactivity of the vagus. The heart is damaged by the chloroform, and adrenalin, whether injected or secreted, may induce ventricular fibrillation. This was beautifully demonstrated by Levy;[213] his analysis applies to the causation of deaths under chloroform and has done a great deal to minimize the dangers of this anesthetic.

Ventricular fibrillation may sometimes be stopped by a strong electrical stimulus applied to the heart, particularly after cardiac massage.[316] Similarly, an intense electrical shock applied to the whole individual may break the irregular circus movement of fibrillation and initiate normal rhythm. Such treatment, though valuable, may itself start ventricular fibrillation if applied in error to a heart which is not in fibrillation. The effect depends on forcing simultaneous contractions in numerous fibers which are in a relatively refractory state. Ventricular fibrillation may also be overcome experimentally by suppressing all contraction with excessive KCl; if this is then antagonized by $CaCl_2$, contraction is resumed at a normal rhythm.[181]

Premature Beats or Extrasystoles.—In the discussion of the refractory period (page 344) experiments on amphibian hearts have been described in which extra beats were induced prematurely by electrical stimulation. Premature beats of a similar type may occur spontaneously in animals and in man, and cause irregularities in the rhythm. They arise in some focus other than the normal pacemaker. The excitability at this focus is presumably abnormally high as the result of some slight modification of the tissue. Extrasystoles are often induced by the action of adrenalin. Sometimes under conditions of heavy work their induction appears to depend on inadequate nutrition and is associated with damaged coronary circulation. Such premature beats indicate damaged hearts. The commoner premature beats are not found during work, but are associated with a very slow pulse during rest. In such cases the main causative factor is not so much the raised excitability of the abnormal focus, as an excessive inhibition of the sino-auricular pacemaker by nervous activity (vagus). These extrasystoles indicate no functional disability. Since extrasystoles arise in abnormal foci they

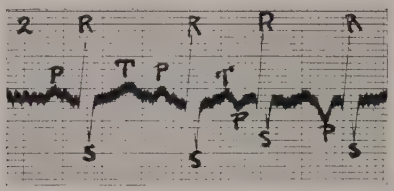


Fig. 122.—Auricular extrasystole. Two auricular extrasystoles following two normal complexes. Note the ectopic origin of the extrasystoles indicated by the inversion of *P*.

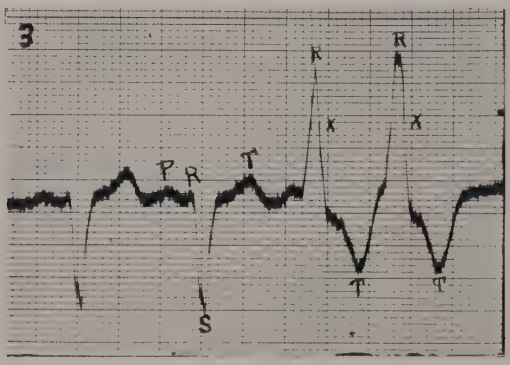


Fig. 123.—Ventricular extrasystoles of right ventricular type.

are called "ectopic" beats. In certain cases the abnormal beats are associated (probably) with errors in conduction, such that "re-entry" and circus conduction are established; a series of abnormal beats may then follow one another at a rapid rate causing a "tachycardia." These may be of auricular or ventricular origin.

Auricular extrasystoles have their origin outside the sinus node and this may sometimes be indicated by a P-wave which is abnormal in contour (Fig. 122). In these cases conduction below the A-V node is normal. When single auricular extrasystoles occur, they may be identified, even in the absence of modified P-waves, by the maintenance of a uniform sinus rhythm, broken only temporarily by the extrasystole and its refractory period. Whether the P-wave is modified or not depends on the distance of the origin of the abnormal impulse from the sinus node.

Nodal extrasystoles may arise in the auriculo-ventricular node. In this case the ventricular portion of the electrocardiogram is normal, but it is not preceded by an auricular wave.

Extrasystoles arising in the *ventricles* result in an abnormal spread of excitation and, consequently, give abnormal electrical complexes. These are designated as of right or left ventricular type according to whether the electrical changes are similar to those seen with right or left ventricular preponderance. Probably, however, the actual origin cannot be predicted, and different origins in one ventricle may give rise to complexes of either type. Fig. 123 shows an electrocardiogram in which the normal beats show *left ventricular preponderance* (marked S-wave in Lead III); the extrasystoles marked X are of the opposite type and show a *right ventricular preponderance*. They are not necessarily of right ventricular origin, but may have originated in some abnormal focus in the left ventricle (compare reversal of the P-wave in Fig. 122 where the focus of excitation was at the end of the auricle opposite the sinus node). A ventricular extrasystole of another type is shown in Fig. 124. This record shows that a ventricular extrasystole has no effect on the rhythm of the pacemaker. The extrasystole starts during the development of the P-wave, but the rhythm of the auricular wave is in no way upset. Long compensatory pauses may follow an extrasystole. They depend on the arrival of a normal impulse in the ventricle while it is still refractory from the extrasystole; the ventricle fails to respond until the following impulse arrives. The condition is

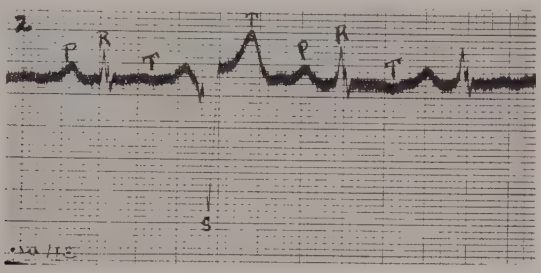


Fig. 124.—Ventricular extrasystole of left ventricular type as shown in records by Lead II.

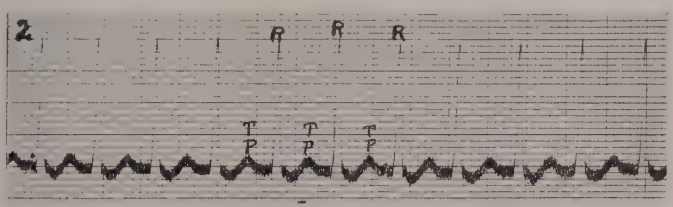


Fig. 125.—Paroxysmal tachycardia. Auricular origin. Note that the *P* deflection falls back on *T*. Rate 200 per minute.

similar to the compensatory pause demonstrable in the frog-heart after a response to an external stimulus (page 344). Such long diastolic pauses may result in a temporary marked fall of diastolic pressure.

Paroxysmal Tachycardia.—Sometimes extrasystoles, usually of auricular origin, follow one another in rapid sequence, and the abnormal pacemaker maintains a fast rhythm far above that of the sinus node. There are usually paroxysms of rapid pulse, starting abruptly and ending abruptly. The attacks may last a few seconds or for days. This condition is called paroxysmal tachycardia; a typical electrocardiogram is shown in Fig. 125. The systolic phase estimated electrically is short (approximately 0.2 sec.), but the systole to cycle ratio is long (approximately 0.66 sec.). The ventricular diastolic period is so short (about 0.1 sec.) that the heart has little rest or time for the metabolic processes of recovery; venous filling is impaired owing to this shortening of diastole, and the contraction is accomplished not only very extravagantly but also very ineffectively. Usually these attacks can be inhibited by vagal action; compression of the carotid arteries above the sinuses (see page 463) may, through reflex vagal discharge, stop the tachycardia, and on resumption of a

beat the rhythm may be normal. If the vagal action so induced reflexly proves inadequate, the injection of a stable acetylcholine derivative (beta-methyl-acetylcholine is more stable in the body than is acetylcholine itself) may bring an attack to a close by its vagomimetic action.

Tachycardia also may be of ventricular origin. Fig. 126 shows such a series of ventricular beats. Little is known of their cause. They may be seen experimentally in animals after injection of adrenalin (particularly in choralose anesthesia); they sometimes develop in animals after experimental aortic lesions have been made, where there is evidence of damage to the endocardium of the ventricles.

The tachycardias, both auricular and ventricular, are probably dependent on a stimulation of cardiac activity by re-entry. This is probably a circus movement not very different from that described for auricular flutter (page 363).

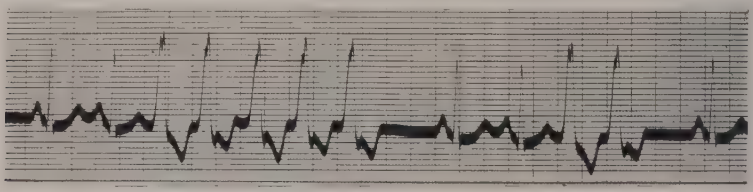


Fig. 126.—Paroxysmal tachycardia. Ventricular origin. Note that the short paroxysm of five beats consists of a succession of ventricular extrasystoles.

NERVOUS AND CHEMICAL CONTROL OF CARDIAC ACTIVITY

Not only is the strength of the heartbeat varied by the initial stretch induced by the degree of filling, and by the chemical condition of the heart (e.g., the staircase phenomenon) but also it is much affected by influences imposed on it by the rest of the body. Nervous effects exerted through the vagus and sympathetic, and modified, as will be seen later, through reflex action, are of great importance. These effects are probably produced through liberation within the cardiac structures of chemical effector substances (mediators). Other chemical effects may be exerted through the blood stream. Of the latter the action of adrenalin is of great importance.

The Course and Distribution of the Efferent Nerves to the Heart.—A schematic presentation of the nerves supplying the heart is given in Fig. 127. Here both efferent fibers and afferent fibers are shown. The latter will be discussed later in relation to reflex control.

Efferent fibers reach the heart in branches from the vagus and from the thoracic sympathetic ganglia. In both amphibia and mammals the efferent fibers of the vagus are preganglionic in character. They do not end in the heart muscle directly but in peripheral ganglia situated in the auricle. From these ganglia postganglionic fibers carry impulses to the sino-auricular and

Fig. 127.—Schematic diagram of the innervation of the mammalian heart. The red continuous lines represent sympathetic (accelerator) preganglionic fibers, which end at cells in the inferior, middle, and superior cervical ganglia and also in the ganglia of the upper thoracic chain. The continuous line running through the chain represents a series of preganglionic fibers connecting with various cells. The dotted red lines indicate the sympathetic postganglionic distribution to the heart. The green continuous lines represent vagal preganglionic fibers and the dotted ones vagal postganglionic neurons, the cell bodies of which are in the heart. The dotted blue lines indicate sensory fibers coursing in the vagus to the medulla (aortic nerve and vagal afferents from the heart chambers) and in the sympathetic strands to the dorsal spinal roots (thoracic I to V). The latter mediate pain. The vagal postganglionic fibers do not go to ventricular muscle, but to the A-V conducting system. The afferent fibers of the vagus arise from cells of the T-shaped unipolar type situated in both the nodose and jugular ganglia.

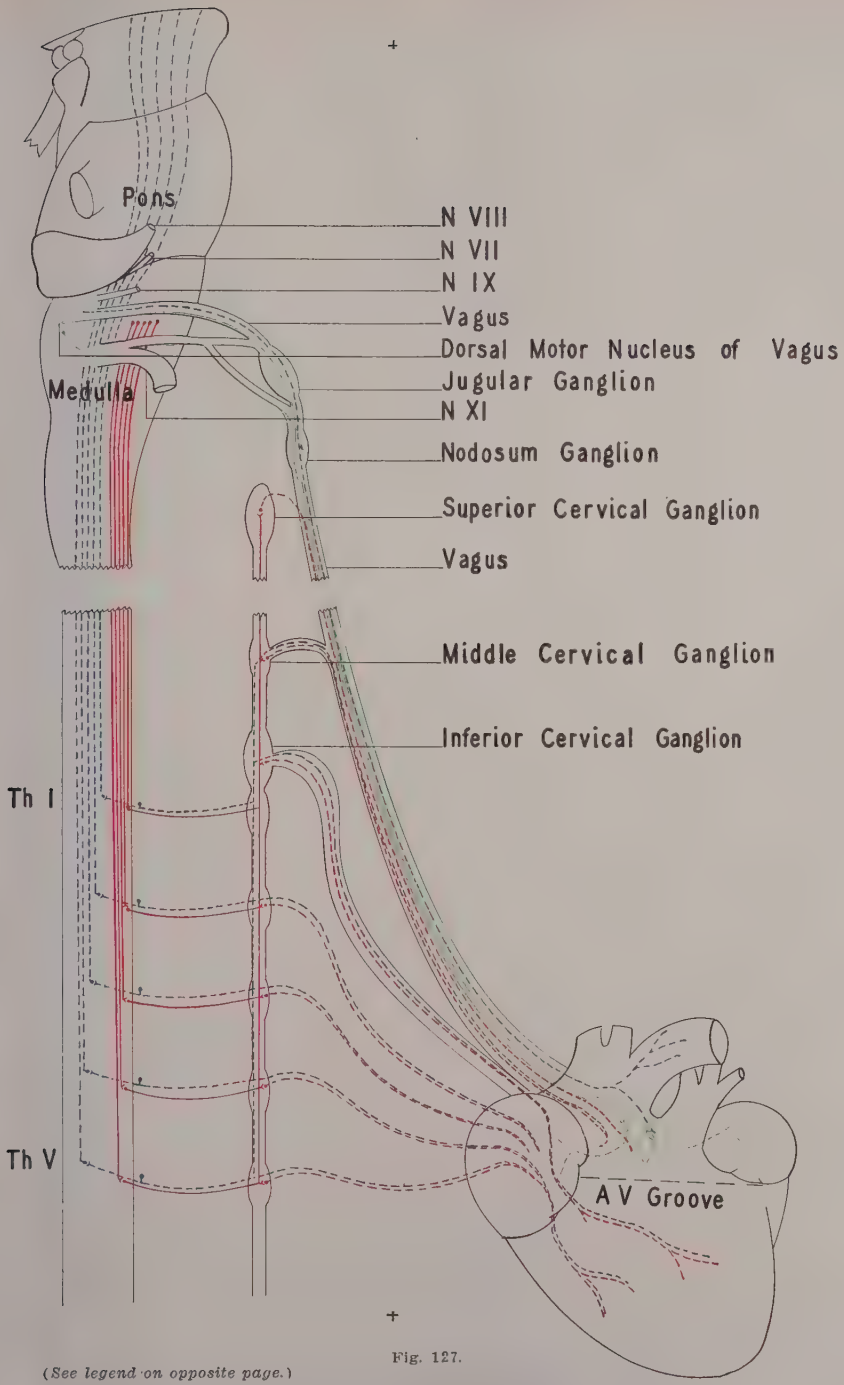


Fig. 127.

(*See legend on opposite page.*)

auriculo-ventricular nodes, to auricular muscle and to the A-V bundle. In the mammalian heart vagal postganglionic fibers do not reach the ventricular muscle. The sino-auricular node and auriculo-ventricular node are innervated by both vagi; however, the right vagus supplies the greater number to the former, the left vagus to the latter. These differences are in line with the development of the sino-auricular node from the right and of the auriculo-ventricular node from the left veins which form the sinus venosus.

The preganglionic fibers of the sympathetic innervation leave the thoracic cord to end round cells of the ganglionated chains in the inferior, middle, and superior cervical ganglia and in the thoracic ganglia as low as the fifth. The greater number of these fibers end round cells in the inferior cervical and upper thoracic ganglia. Postganglionic fibers are distributed directly to the heart and probably supply muscle cells as well as nodal and conducting tissue. Some fibers supply ventricular muscle. Both the vagus and sympathetic nerves belong to the autonomic system (see Chapter XVI).

The Action of the Vagus.—The vagus exerts a considerable persistent or tonic effect in many animals. The effects of its action may therefore be shown either by removal of these tonic effects by section, or by inducing hyperactivity through direct stimulation. Activity of the vagus slows the cardiac rhythm by affecting the pacemaker. It also causes a weakening of the contraction of the auricles, and this effect is associated with a shortening of the refractory period of auricular muscle. In contrast the relative refractory period of the pacemaker is probably lengthened. Vagal activity also slows the rate of conduction of impulses through the auricle and through the bundle of His. The A-V (P-R) interval is therefore increased. The ventricles are affected only indirectly, since the fibers are not distributed to them. Their rhythm is slowed (through the effect on the pacemaker) and the long interval between beats provides favorable conditions for premature beats or extrasystoles of ventricular origin. The force of the ventricular contraction is normally much increased, owing to the greater filling that results from the longer diastole.

The tonic discharge of impulses over the vagus to the heart is not readily demonstrated by recording action potentials from the nerve. This is mainly due to the fact that the vagus is a large nerve containing several groups of afferent and efferent fibers which are tonically active. Further, the impulses which exert the tonic action on the heart are probably not numerous, for artificial stimulation of the vagus in a cat at a rate of 1 stimulus a second suffices to produce a 15 per cent slowing of the pulse rate. The effect of section of the vagi, which may give a considerable increase in pulse rate, can be demonstrated to be due to removal of tonic impulses, since (1) it may be produced by freezing the nerves, thus paralyzing them without stimulation, and (2) a similar effect may be produced by giving atropine which abolishes the cardiac effects of peripheral stimulation of the cut vagus. Atropine interferes not only with vagal action but also with the action of acetylcholine on the heart. Its effect is peripheral and appears to depend on blocking the action of the chemical mediator liberated at the endings of the vagal postganglionic fibers. As already pointed out (page 178), there is excellent evidence that this mediator is acetylcholine.

The general subject of chemical mediation of autonomic impulses is discussed in Chapter XVI, to which the reader is referred. In this place it is of interest to note that the first definite evidence for the existence of chemical mediators was secured in a study of the effect

of vagal stimulation on the frog's heart (Loewi[222]). There is evidence[114, 212] that there is an intimate relation between potassium salts and acetylcholine. The latter is apparently liberated by the action of the former. This is of interest in connection with Howell's findings which were reported in 1906.[184] They led him to attribute the inhibitory effect of the vagi on the heart to the liberation of potassium.

The Effect of Vagal Activity on Pulse Rate.—A marked tonic activity of the vagi is normally found in animals adapted by training to endure prolonged exercise.[68] Thus the pulse rate in the tame rabbit is fast (approximately 205 a minute), and the heart is small. Section of the vagi produces only a relatively slight acceleration (an increase to 321 or a change of 56 per cent), since their tonic activity is low. On the other hand, the resting pulse rate of the hare is much slower (64 a minute), the heart is larger and the effect of vagal section considerable (an increase to 264 or a change of 312 per cent). Similarly the pulse rate is said to be unusually slow in race horses and in man pulse rates below 50, or even below 40, per minute are common in athletes trained for endurance contests. These slow pulse rates are a true *bradycardia* and are accompanied by normal electrocardiograms. Records from a slow pulse of this type are reproduced in Fig. 128. If the rhythm is slow and the cardiac output per minute is normal, the amount expelled per beat must be greater than normal, and the heart is usually large.

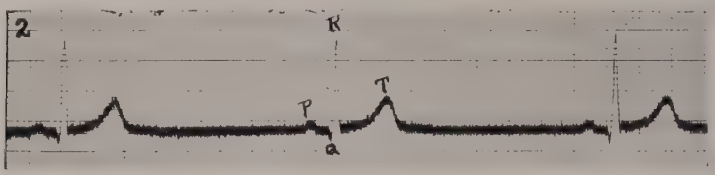


Fig. 128.—Sinus bradycardia. Rate 32 per minute. Note the normal appearance of the electrocardiogram. *P-R* interval = 0.17 second.

With vagal slowing of the pulse diastole is lengthened much more than is systole, so that the ratios of systole/diastole and of systole/cycle are reduced. Thus in Fig. 128 the interval from the start of Q to the end of T is 0.44 second as compared with a normal value of about 0.35 second. This electrical accompaniment of ventricular systole lasts only 23 per cent of the cycle as compared with a normal value of about 38 per cent. In such a heart the diastolic periods during which the ventricle is filled last then for over 46 seconds in any minute, and only 37 seconds at a more normal pulse rate.

The tonic discharge of vagal impulses maintains a relatively slow heart rate and increases in the activity of the vagus induced reflexly may produce marked slowing of the pulse. Rarely do they cause complete cessation of the beat. The normal mammalian heart can be stopped by excessive direct electrical stimulation (faradization) of the vagus, but it is not possible to stop it permanently in this way. If the vagi be stimulated by strong repeated electrical currents, heart activity may be completely inhibited for many seconds, but ultimately the vagal effect fatigues and the cardiac rhythm gradually returns toward a normal rate. The heart is described as "escaping" from the vagal effects. This escape is believed to be due to a temporary exhaustion of the mechanism liberating the chemical mediator (probably acetylcholine). Instances of such escape may be seen in a later figure (Fig. 156, page 418). Since stimulation of the right vagus in a dog is apt to affect particularly the sino-

auricular node, escape may occur with a rhythm originating in the auriculo-ventricular node and therefore be limited at first to the ventricles. With stimulation of the left vagus the main effect may be a blocking of conduction at the auriculo-ventricular node and accordingly escape may first appear in the auricles (see Fig. 156).

The Effect of Vagal Activity on Auricular Contraction and Conduction to the Ventricle.—Allusion has already been made to the fact that the left vagus has a considerable distribution to the auriculo-ventricular node, so that stimulation of this nerve may cause auricular escape with (for a while) continued ventricular inhibition. In effect this is a condition of heart block. On the

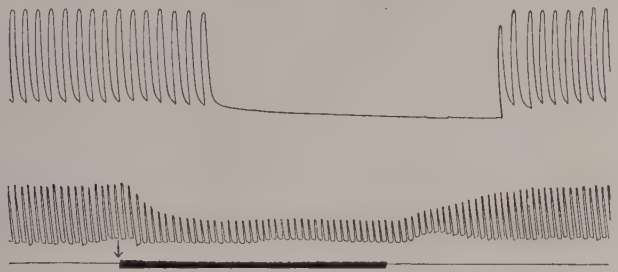


Fig. 129.—Tracing to show that vagus stimulation may diminish transmission from auricles to ventricles. It shows the effect of stimulating the left vagus on partial (2/1) block produced on heart of turtle by application of clamp at auriculo-ventricular junction. Stimulation at ↓ depressed the conductivity and weakened the auricular contractions (lower tracing) without slowing their rate. The result was an increase in the degree of block with cessation of ventricular contractions (upper tracing). Initial auricular rate = 35 per minute. (From Garrey.)

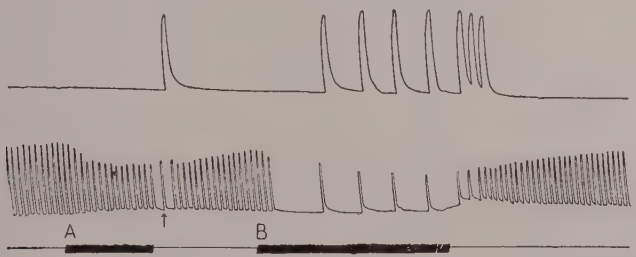


Fig. 130.—Tracing to show that vagus stimulation may facilitate transmission from auricles to ventricles. It shows the effect of right vagus stimulation on heart-block produced in the turtle by a clamp. Upper tracing records ventricle; lower tracing, auricles. Weak faradization of the right vagus nerve beginning at *A* affected the degree of block only at ↑, when a lengthened period between auricular contractions caused a single ventricular contraction. At *B* stronger faradization of the same nerve produced marked slowing of the auricles, in consequence of which the block disappeared and the ventricles contracted after each auricular contraction. Block reappeared when the rate again became rapid. Initial auricular rate = 36 per minute. (From Garrey.)

other hand, the slower rhythm of contraction in the auricle induced by the vagus allows a longer period of recovery which may be of benefit to damaged tissue. Consequently, under some conditions, vagal stimulation may remove a preexisting block. The point is illustrated by Figs. 129 and 130. Fig. 129 shows the effect of clamping the auriculo-ventricular groove in a turtle's heart. It is seen that moderate pressure interfered with A-V conduction to the extent that a 2 to 1 block was set up. Only every other auricular beat was fol-

lowed by a ventricular systole. Under such conditions the auriculo-ventricular conduction, when completed, is abnormally slow. Stimulation of the left vagus weakened the auricular contraction and depressed A-V conduction. After a considerable latency complete heart block supervened. In Fig. 130 compression of the junction was in itself adequate to produce complete heart block. Weak stimulation of the right vagus at *A* had no effect on the ventricle except a secondary one dependent on slowing of the auricles. In this case impulses from the auricles impinged on the conducting tissue at a lower frequency and so allowed the compressed tissue more time in which to recover its excitability. It was then able to transmit them to the ventricle. At *B* stronger stimulation of the vagus, which greatly slowed the rate of auricular contraction, allowed still greater recovery and so for a time completely removed the block.

The effect of vagal action on weakening the auricular contraction with shortening of refractory period and slowing of conduction of impulses is important. These are the changes which favor the setting up of re-entry and generation of circus movements. Ventricular fibrillation is apt to develop during induction of anesthesia by chloroform, particularly if an injection of adrenalin has been given. The combined effects of these substances probably cause in the ventricle changes in the rate of conduction and in refractory period, which favor re-entry (see page 363).

Fig. 131.—Action potentials from cardio-accelerator sympathetic nerves. Volleys of impulses occur with each pulse (upper record). These volleys are inhibited with each inflation of the lungs (upward movement of the lowest white line). (From Bronk: Harvey Lecture on the Nervous Mechanism of Cardio-Vascular Control, Baltimore, 1934, The Williams and Wilkins Company.)

The Action of the Accelerator Nerves.—The accelerator nerves, like the vagal fibers, are normally in tonic activity. The effect this produces on the pulse rate is much less marked than that of the vagi and no conspicuous change in pulse rate is seen when the accelerator nerves are sectioned. The fibers, however, may be readily isolated and the presence of impulses constantly proceeding distally in them may be demonstrated electrically. These impulses tend to be modified reflexly and to be grouped according to both respiratory and pulse rhythms (Fig. 131).

When the accelerator nerves are isolated and stimulated electrically their effect is induced only slowly, so that no change in pulse rate is usually seen for five to ten seconds. The effect also lasts many seconds after the end of stimulation. Stimulation produces not only acceleration but also a more forcible contraction of both auricles and ventricles. The mechanical efficiency (ratio of the work done to the total energy production) is also improved. Probably the optimal pH for effective contraction is changed to the acid side.[246] The cardiac muscle is rendered more excitable and premature contractions of ventricular origin are apt to occur. The increased force of the heartbeat may not be in evidence if the change in rate is considerable, for the degree of filling (and the effect of the initial diastolic stretch) is thereby reduced.

The acceleration of the heart produced by sympathetic stimulation shortens diastole more than systole, so that the ratios of systole/diastole and of systole/

cycle are increased. It has been shown by Wiggers that increases in pulse rate produced by accelerator stimulation (or by adrenalin injection) are associated with systolic durations which are shorter than those seen with similar pulse rates produced by other means. While in most respects the actions of the vagus and the accelerator nerves are opposed to one another, in respect to their effects on the systole/diastole ratio for any given pulse rate they are to some extent synergic.

Sympathetic activity is also mediated by a chemical substance, sympathin (see Chapter XVI). Its slow accumulation around the fibers and slow removal would explain the latent period, the long after-effect, and the summated effect of repetitive stimulation which is observed and which resembles that (to be described later) in vasoconstrictor nerves. Accelerator stimulation produces effects which resemble those produced directly on the heart by adrenalin.

The work of Rosenblueth and Simeone[266] demonstrated that as far as the effects on the frequency of the heart's contractions are concerned, simultaneous stimulation of the vagus and accelerator gives a response which appears to be the resultant of two opposed processes. The percentage slowing produced by any given vagal stimulation is the same whether the accelerator is being stimulated or not. The normal cardiac rhythm is evidently affected by two systems (acceleratory and deceleratory) acting simultaneously, but when reflex changes are induced one of these is increased and the other is reduced. However, in one respect these nerves are synergic, for both tend to reduce the systole/cycle ratio. Consequently, at any given pulse rate produced by balancing these two influences the systolic duration should be shorter, the greater the degree of tone in the two nerves. The work of Bronk[52] has shown that many fibers in the accelerator nerves fire synchronously owing (1) to the coordination produced by one preganglionic fiber activating many postganglionic neurons, and (2) to a synchronous activity often imposed on the preganglionic fibers by higher centers. The frequency of the naturally occurring impulses is from 1 every 3 or 4 seconds to 15 per second. Electrical stimulation of the cut accelerator at the lower of these frequencies produces no demonstrable effect on pulse rate, but at the higher frequency acceleration is induced. Whether variations in the tonic discharges (vagal and sympathetic) exist for any given pulse rate is not known.

Humoral Factors.—Adrenalin discharged into the blood stream has powerful effects on the heart. They are of the same type as those produced by accelerator stimulation. Such effects are most readily demonstrated when the vagi have been cut. Thus if the peripheral end of a splanchnic nerve be stimulated in a decapitate cat the pressure first rises as a result of vasoconstriction in the splanchnic area produced by vasoconstrictor impulses. This is followed by a superimposed secondary rise which is due to the effects of liberated adrenalin on the heart, namely, an increase in the rate and force of contraction (see Fig. 171). (In the intact animal adrenalin so liberated, or injected intravenously, may initiate the same effect, but the consequent rise in arterial pressure produces secondarily a reflex slowing of the heart by the vagus.) If the heart is completely denervated and time is allowed for the nerves to degenerate, it becomes hypersensitive to adrenalin, and extremely small doses may produce marked changes in pulse rate. Under such conditions it makes an excellent indicator of adrenalin secretion. Sympathin produced by sympathetic stimulation in other parts of the body may accelerate the heart, but quantitatively to a much less extent. Although the effects of sympathin may be demonstrated on the sensitized denervated heart, it is doubtful whether they are significant in the normal animal. Thyroxin also increases the pulse rate, possibly by sensitizing the heart to other agencies.

CHAPTER XXXI

THE HEART AS A PUMP

The heart has been considered so far as an independent unit. Attention will now be directed to the action of the heart as a pump, and the resulting effects on the emptying of the veins and the filling of the arteries. This subject already has been briefly referred to in outline. Here it will be treated in more detail and in relation to the pressure and volume changes induced in the heart by its contraction. The time relations of the various events of the cardiac cycle will first be considered, then the actual quantitative output of the heart and the factors which modify it will be discussed.

THE CARDIAC CYCLE

The events of the cardiac cycle may best be considered first by study of the pressure changes in the auricles and ventricles, and by relating the times at which these changes occur to the waves of the electrocardiogram. The latter serves as a useful time scale. The events may then be considered in relation to the systemic blood vessels and the effects produced on arterial and venous pressures.

Methods of Recording Intra-Auricular and Intraventricular Pressures.—In the earlier work, such as that of Marey, intraventricular pressure was recorded by the introduction of a long tube, or "intracardiac sound," through a large vessel into the heart and this was then connected with a tambour. A tambour is a simple cup covered with rubber (or some other elastic material); any rise of pressure in the system causes a bulging of the rubber, which movement may be recorded mechanically by a lever or optically by a mirror. The early observations were made on horses, since the inertia of the instruments was recognized as a source of error, and the slow pulse of the horse minimized such errors. The introduction of tambours carrying mirrors, which record their movements, known as optical manometers, put the whole matter on a far more accurate basis, though the difficulty of obtaining intracardiac records with a normal chest and normal subatmospheric intrathoracic pressure remained. The manometer recently introduced by Hamilton,[158] which has a high natural frequency, even when connected to the artery by a narrow needle, has assisted in overcoming these difficulties. The optical manometers used for intraventricular and intra-auricular pressure determinations are the same, except for modifications of their sensitivity, as those used for blood pressure (see page 416). By recording simultaneously pressures in the auricle, ventricle, and aorta, and by comparison of these with the electrocardiogram and with records of heart sounds, much may be learned regarding the time relations of ventricular contraction.

In Fig. 132, semidiagrammatic composite curves are presented to demonstrate the normal relations of the pressure changes in the left auricle and ventricle, and in the aorta just distal to the valves. The ordinate scale on the left shows the pressures in relation to atmospheric pressure; on the right the scale is in absolute values. Since the heart is contained in the thorax where the pressure is subatmospheric, the actual pressure developed by the heart should be considered in relation to this intrathoracic pressure. The curves drawn represent values to be anticipated in man with a normal blood pressure of 102/60 and a pulse rate of 65. The lines above show time intervals of importance in this diagram to indicate their normal *order of magnitude* at such a pulse rate.

Compare first the pressure curves from the left auricle and ventricle. In this and other comparisons the electrocardiogram may be used as the time standard. The start of the P-wave indicates the commencement of excitation in the auricles. A few hundredths of a second later a rise in pressure lasting about 0.1 second develops in both auricle and ventricle; this must be due to the auricular contraction and the delay is due to the *latent period* between the electrical and mechanical changes. This latent period is partly real in that excitation precedes contraction but mainly it is an artifact in that the mechanical changes do not readily develop measurable pressures until excitation has spread

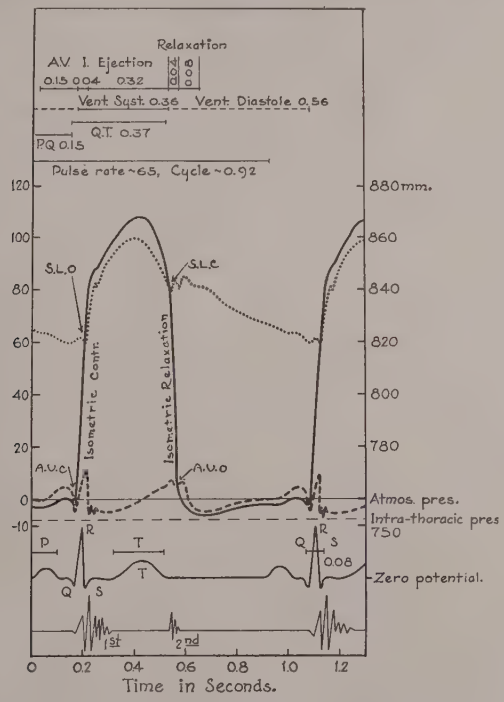


Fig. 132.—Diagrammatic representation (from below upwards) of heart sounds, electrocardiogram, left intra-auricular pressure (broken line), left intraventricular pressure and aortic pressure (dotted line) in man with a pulse rate of 65. Abscissae, time; ordinates, pressure in mm. Hg, relative to atmospheric pressure on left, to absolute on right. Time values represent only orders of magnitude of intervals which vary considerably. Note that the mechanical changes of ventricular systole start 0.02 sec. after the beginning of the Q-wave. *S.L.O.* and *S.L.C.* indicate the opening and closing of the semilunar valves. *A.V.C.* and *A.V.O.* indicate similar movements of the auriculoventricular valves.

over a large part of the muscle. The rise in pressure developed is similar in both auricle and ventricle, since the auriculo-ventricular valve is open and the two chambers are in open communication with one another. Actually the total energy is somewhat greater in the auricle, for flow occurs from the auricle to the ventricle, but the resistance in the valvular orifice is low and the difference in pressure is not readily demonstrated. Auricular contraction reaches a peak

and begins to subside, and during this subsidence the auricular pressure tends to fall below that in the ventricle, because as the auricle relaxes, the mitral valve tends to close and to maintain the original pressure in the ventricle; again the difference is small and not readily demonstrated, but a presystolic shutting of the mitral (or of the tricuspid) valve may give rise to sound vibrations of low frequency which may precede not only ventricular contraction but even ventricular excitation (Q). This early valvular closing, of obvious functional value, is rendered possible by the delay of conduction at the auriculo-ventricular node indicated in the E.C.G. by the interval from the end of P to the start of Q. The closing of these valves, however, more commonly occurs later with the onset of ventricular contraction.

Auricular contraction continues to subside, while ventricular excitation starts, but the mechanical consequences of ventricular contraction are not recordable till somewhat later (about 0.02 sec.), when the ventricular pressure starts to rise abruptly. This occurs usually during the upstroke of the R-wave. The apparent latency is again largely an artifact and varies with the sensitivity of the recording apparatus, as was emphasized by Einthoven. Any real latency, though probably present, is likely to be of a lower order of magnitude. As soon as intraventricular pressure rises the mitral valve closes, if it has not already done so, and the pressure curves of the auricle and ventricle are now quite different. The rise in pressure within the ventricle causes the valves to bulge into the auricle producing a short initial rise in the auricular pressure curve, but the main effect of the ventricular contraction is to cause a fall of pressure in the auricle, in spite of the damming back of blood into it. This fall is probably due to the movement of the auriculo-ventricular margin towards the apex, as the ventricle shortens. This movement must lengthen the auricles, since their venous orifices are relatively fixed, and the consequent increase in their capacity causes the fall in pressure. Later, as the inflowing blood, which is dammed back during the ventricular systole, increases, the pressure again rises. With ventricular relaxation the base of the ventricle tends to move upwards again, as recoil ceases and later as the ventricle fills. The resultant shortening of the auricle tends to produce a positive pressure wave. As the main part of this change, however, is contemporaneous with ventricular filling, the positive wave is transient, and merely forms an exaggeration or duplication of the wave due to auricular filling. When ventricular relaxation is complete, the intraventricular pressure falls below the auricular pressure level, the mitral valve opens, the blood collected in the auricle as well as that continuing to return from the lungs enters the ventricle, and again the pressure changes in the two connected chambers vary in unison.

The intra-auricular pressure curve recorded in the left auricle shows, therefore, three main positive waves. The first is due to auricular contraction, the second to the initial bulging of the mitral valve; the third, which is more complicated, depends on the accumulation of blood in the auricle during ventricular contraction and on the impulse transmitted to this accumulated blood when the recoil reaction of the ventricle ceases and the base of the ventricle tends to return to its normal position. In the negative phases pressures drop below the atmospheric but not below the intrathoracic level. The initial rise of pressure due to auricular systole may cause some regurgitation of blood into the veins, but probably not much, owing to the contraction of the auricle round the venous

orifices and to a partial valvular action that results from a somewhat oblique entry of these veins into the auricle. The pressure changes in the right auricle are very similar to those in the left. Although the pressures in the right ventricle do not rise nearly so high during systole as those in the left, the general relationship of the auricular and ventricular pressures on the right side is the same as that described.

Comparing intraventricular pressure with aortic pressure and starting again in diastole, the aortic pressure is seen to be very different from that in the ventricle, which is at this time in open communication with the left auricle and is filling from the pulmonary veins discharging through the auricle. The aortic semilunar valves are closed. When the ventricle starts to contract, the pressure within it is rapidly raised, but all the valves remain closed until the pressure is raised above that in the aorta, when the semilunar valves open. This period of contraction is one of rising tension, but during it there are no changes in the volume of the contents of the ventricle and the lengths of the fibers remain unchanged; merely their tension is altered. It is, therefore, a *period of isometric contraction*. See Fig. 132. Under normal conditions in man it lasts 0.02 to 0.06 second, most commonly 0.04 to 0.05 second. Exact values are hard to give since the interval is not readily determined in man, and in animal experiments interference with the thorax may not leave conditions normal. Following the opening of the semilunar valves, blood is forced out rapidly into the aorta. The pressure in that vessel is raised and the period of ejection commences. Ejection is very rapid at first and decreases somewhat in the later stages of systole. If intraventricular pressure be measured close to the cardiac side of the semilunar valves when the blood has already been set in motion, the pressure curve resembles that of the aorta closely, since there is little loss of free energy between the ventricle and aorta. If, however, the pressure curve be obtained from a point near the apex, where the fluid movement is negligible, differences of pressure must exist, as indicated in Fig. 132.

Though the free energy available in the two places is almost the same, in the aorta some of this energy is present as velocity energy, so that the pressure energy is lower, and the difference in the two pressures is a measure of the velocity of flow. The picture is, however, complicated in that the pulse wave is reflected back from such points as the bifurcation of the abdominal aorta, and these reflected waves must be again reflected from the heart towards the aorta in the later part of systole. Such waves develop at different points at different times and complicate the issue. The curves represent differences in pressure of the type and magnitude described by Wiggers, an example of which is reproduced in Fig. 133, taken from one of his earlier communications[312] (at present he doubts their validity) and representing differences smaller than those reported (with an intact chest) by Hamilton and Brackett.[157] Though the magnitude of the discrepancies between the aorta and the apical area of the left ventricle is controversial, it is certain, on hydrodynamical grounds, that the two pressure curves must diverge significantly.

Eventually the gradual cessation of muscular activity in the ventricle supervenes, the pressures in both the ventricle and aorta fall, the former faster than the latter, until the pressure in the ventricle is the lower, when the aortic valves close. Tension in the ventricular muscle continues to fall but no change in ventricular volume occurs, until the pressure has fallen below that in the auricle and so has permitted the mitral valve to open. This period is that of *isometric relaxation*. During diastole blood stored in the left auricle as well as that returning in the pulmonary veins enters the ventricle. The initial

pressure in the left auricle is relatively high and inflow is rapid, but the blood that had been stored in the auricle is emptied into the ventricle, tending to lower slightly the pressure in the former and raise it in the latter. Ventricular filling therefore becomes much slower and represents merely inflow from the pulmonary veins. If the ventricular pressure rises, even this inflow may be slowed. If the pulse rate is slow and diastole long, inflow may be much slowed in the latter part of diastole, and the period is then called one of *diastasis*. When the auricle contracts in the next cycle it forces some additional blood into the ventricle, not a large but a significant proportion of the total, and assists in the closure of the mitral valve. The pressure changes in the right ventricle and pulmonary artery are of a similar type to those on the left side but proceed at a much lower pressure level. The pulmonary circuit will be discussed separately later.

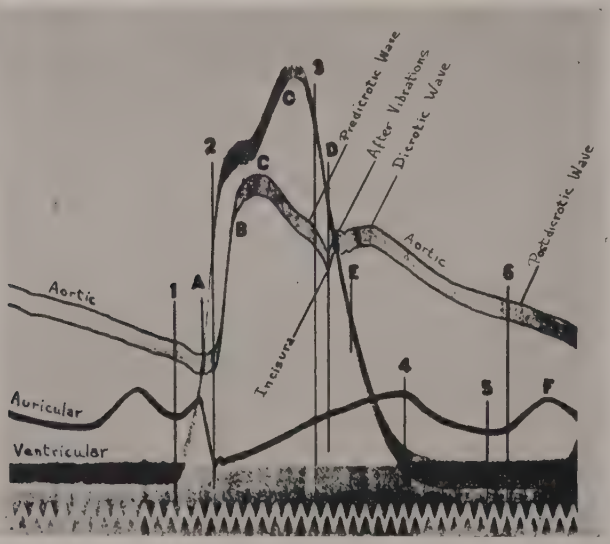


Fig. 133.—Simultaneous records of aortic (upper), left auricular (middle) and left ventricular (lower) pressures to show their time relations. Period *1-2* is the isometric phase of ventricular contraction; *2-3*, the expulsion period; *3-D*, the protodiastolic fall of pressure preceding closure of the aortic valves at *D*; *D-4*, isometric relaxation; *4-5*, period of rapid inflow. The time intervals indicated below are 0.02 sec. (From Wiggers: Am. J. Physiol. 56: 3, 1931.)

The events just discussed allow a further subdivision of the cardiac cycle into various phases. Ventricular systole may be divided into the *isometric period of rising tension* (about 0.05 second), and a *period of ejection*, rapid at first and slower later, lasting through the rest of systole with a duration (at a pulse rate of 65) of about one-third of the cycle length. Ventricular diastole may be divided into a *protodiastolic period* when pressures are falling rapidly in the ventricle and aorta before the aortic valves have closed (0.04 sec. according to Wiggers[112]), an *isometric relaxation phase* when the tension in the ventricle is falling but all valves are closed (about 0.08 sec.), and a *period of filling*. The duration of this last period varies greatly with the

duration of the cycle. It may be roughly divided into an initial *period of rapid filling*, a later *period of diastasis*, and a *period of auricular systole*, but the division into the first two periods is entirely arbitrary. The early rapid filling of the ventricles, dependent on the necessary damming back of blood in the auricles during ventricular systole, is, however, of considerable physiological importance. As the pulse rate is increased, and diastole shortened, it is the period of diastasis that is reduced, and, consequently, the filling of the ventricle is not much hampered.

Action of the Valves

The valves of the heart, mitral, tricuspid, and semilunar, are set in orifices. The diameter of the chambers beyond them is greater. In the case of the auriculo-ventricular valves such a condition may be without significance, but in the aorta it results from the definite broadening of this vessel just above the valves in the sinuses of Valsalva, and hence may be presumed to have possible functional significance. The functional significance of this anatomical arrangement probably depends on the presence of eddy currents, which are readily generated when fluid is forced through an orifice into a broader vessel. Such

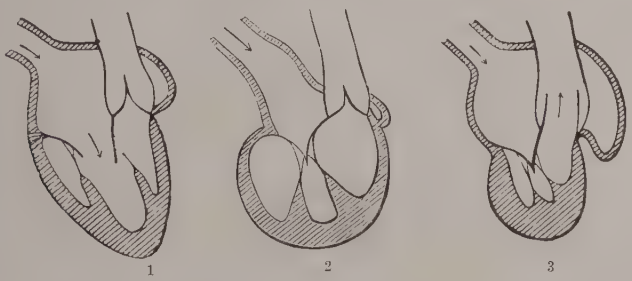


Fig. 134.—Diagram to show the positions of the cardiac valves: 1, during diastole; 2, during isometric contraction; 3, during the expulsion period.

eddy currents are important because they keep the valves floating in the stream and prevent their being pressed against the side walls; not only are the valves in a position to close more rapidly, but also the semilunar valves of the aorta are prevented from obstructing the origin of the coronary arteries. Evidence that such eddy currents are generated and that they act in this way is provided in recent moving picture films made of the action of the ox heart when intermittently distended by artificial means. In spite of the relaxed state of the muscle in such hearts the valves function adequately, and the maintenance of the cusps in a position ready for rapid closure by the action of eddy currents is clearly demonstrated. The position of the valves is shown diagrammatically in Fig. 134. The valves open when the pressure in the proximal chamber exceeds that in the distal, whether this condition develops from a rise in pressure in the proximal chamber (as in the opening of the semilunar valves by the rise of pressure in the ventricle) or from the fall of pressure in the distal chamber (opening of mitral and tricuspid valves). The valves close when the pressure in the distal chamber exceeds that in the proximal whatever the cause of the difference. Closure of the semilunar valves is certainly the result of the fall of pressure in the ventricle; the closure of the mitral and tricuspid valves may

certainly result from the rise of pressure in the ventricle, but may also result from a fall of pressure in the auricle. The latter is a logical cause which cannot fail to operate unless the fall of pressure in the auricle is very small. The complete closure of these valves as a result of auricular relaxation would be difficult to demonstrate experimentally, and has not been so demonstrated conclusively.

The large auriculo-ventricular (mitral and tricuspid) valves are supported by the chordae tendinae which are attached to the papillary muscles. Consequently, the valves are prevented from bulging to any great extent into the auricles as the ventricles shorten; the contraction of the papillary muscles compensates for this shortening.

The Heart Sounds

Two distinct sounds may be heard by applying the ear, or a mechanical sound transmitter, the stethoscope, to the chest. The first occurs at the beginning of ventricular systole and is best heard over the site of the apex beat. The second occurs at the end of systole and is best heard in the sternal region near the second intercostal space. A third heart sound is in rare cases detectable in diastole; less infrequently it can be recorded though not heard.

Graphic Records of Heart Sounds.—Heart sounds may be fairly readily recorded, and the records are often of assistance in precisely timing the sounds. Such records, however, differ considerably from the sound as heard, for the ear is relatively insensitive to the low primary vibrations of the heart sounds, and exaggerates the higher overtones, and the higher independent notes that may be generated in a murmur. The ear distinguishes and analyzes these higher notes which, in a graphic record, may merely appear as inconspicuous small secondary vibrations fused more or less irregularly with larger vibrations of a much lower pitch. Apart from greater accuracy in timing, the recording of sounds does not add greatly to the analysis, unless electrical reproduction is used, where, by the appropriate introduction of filters, notes in various ranges may be exaggerated as desired. By such means accurate analysis may be laboriously attained.

The simplest method of recording is by means of a tambour attached to the chest wall and connected by a short length of rubber tubing (preferably of large bore) to an optical segment capsule covered with a sensitive membrane. A segment capsule is a simple small tambour with one part of the edge flattened to form a chord of the circle; this device increases its sensitivity. A side-tube on the connecting tubing is fitted with a clamp; if a fairly wide opening is left to the air the slow waves created by the large movements of the chest are damped out and only the faster vibrations are recorded. The membrane used consists of light mica (pattern of O. Frank) or of a very thin rubber membrane made from a bubble of rubber cement (pattern of Wiggers and Dean[317]). In either case a very light mirror is used to record the movements of the membrane, and the membrane must be enclosed within a boxlike cover, with only a small hole to allow pressure equilibration, as otherwise the front of the membrane picks up extraneous sounds from the room. Wiggers' type has been improved by vulcanizing the rubber membrane and utilizing damping plates, so that a natural instrumental frequency of over 300 per second has been attained.[99]

In using electrical methods the sounds are best picked up by a condenser microphone, and may then be amplified and filtered so as to include only those sounds that fall within any desired range. They may be recorded by an oscillograph, or by a string galvanometer if this has a sufficiently short (but therefore relatively insensitive) string of high frequency. In some set-ups the sounds are amplified electrically, taken to a loud speaker, and the amplified sounds there generated are transmitted by air (through a short distance) to an optical capsule. The last method has given valuable results, though reconversion to air transmission is theoretically unsound.

Auscultation.—The vibrations generated in the heart are transmitted to the chest wall and are modified by the resonance of these structures; they tend to be conducted along the

ribs, as well as along columns of moving fluid in the direction of the movement. The sounds heard are modified by the resonance of the particular receiver used, so that the observer should habituate himself to the receiver of his own choice. The varied selections made by different people in this regard probably depend on the varying sensitivity to sounds of different pitch of different observers and the consequent advantage or disadvantage of accentuating certain notes.

The First Heart Sound.—The first heart sound consists of irregular vibrations, mainly of a frequency of 30 to 45 a second. These may be grouped into preliminary vibrations, main vibrations, and final vibrations. They probably originate in three ways: (1) from the vibrations of the auriculo-ventricular valves during and after closure, (2) from vibrations set up by eddies in the stream ejected through the aortic orifice into the broader sinuses of Valsalva, and (3) from vibrations in the muscle fibers themselves, generated by passage from relaxation to tension. In the first sound, as developed in the ventricle and heard at the apex, the closure of the auriculo-ventricular valves probably gives rise to the one or two small slow initial vibrations. The first sound with a single initial vibration may be entirely induced by ventricular contraction, as may be seen in Fig. 135, where the records were obtained in a case of heart-block, with dissociation of auricular and ventricular contraction, so that auricular involvement could be excluded. Auricular contraction gave rise, however, to

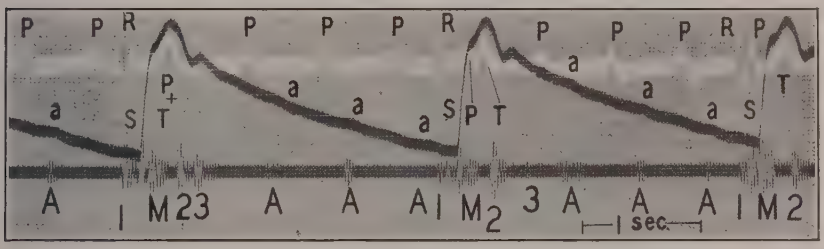


Fig. 135.—Records of heart sounds and radial pulse with electrocardiogram (from below upwards) obtained in a patient with complete heart block. The heart sounds are labelled *1*, *2*, *3*, and *A*, and an abnormal murmur due to a valvular lesion is indicated by *M*. The sound *A* is generated by auricular changes, probably relaxation of the auricle. Auricular activity also causes pressure waves transmitted to the radial and occurring there at the time of the auricular sounds *A*. These are labelled *a*. The waves of the electrocardiogram above are labelled conventionally. In the first cycle the first sound is more intense, since auricular contraction happened to occur at an almost normal time and to improve ventricular filling; the small auricular sound is fused with it. In the last cycle the first sound is entirely ventricular in origin and less intense. Vertical lines on the record indicate time intervals of 0.04 second. (Unpublished record by Wolferth and Margolies, see these authors: Arch. Int. Med. **46**: 1048, 1930.)

separate weak sounds which may be seen to follow the P-waves. Not uncommonly, however, the initial vibrations of the first sound develop before ventricular contraction, and even before the Q-wave of the E.C.G. Under such circumstances these initial vibrations must be partly dependent on auricular relaxation. The development of auricular contraction also causes sound vibrations (as in Fig. 135), but these sounds cannot usually be heard or recorded from the chest wall in a normal individual; they can, however, be readily heard and recorded in subjects in which the chest wall has been partly removed (e.g., after Estlander's operation) and can be recorded even in the normal subject from receivers introduced into the esophagus so that they are in close contact with the auricles.[295] These auricular sounds may occasionally be so exaggerated that they modify the first heart sounds as heard and recorded in a normal subject.

The main vibrations of the first sound develop usually towards the end of the R-wave, considerably after the beginning of the ventricular contraction which, according to Wiggers,[313] develops 0.02 to 0.03 second after the beginning of the electrical changes, or on the upstroke of the R-wave. These vibrations probably depend on factors 2 and 3. The fluid eddy factor may be demonstrated

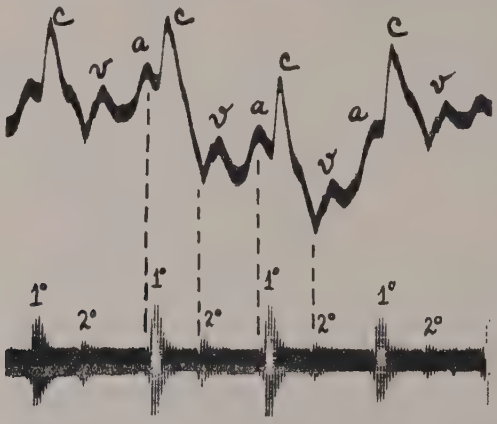


Fig. 136.—Records of heart sounds (lower) and pressure waves of jugular pulse (upper). The first and second sounds are indicated as well as the *a*, *c*, and *v* waves of the jugular pulse. (From Battro, Braun Menéndez and Orias: J. de Physiol. et de Pathol. Gen. 33: 51, 1935.)

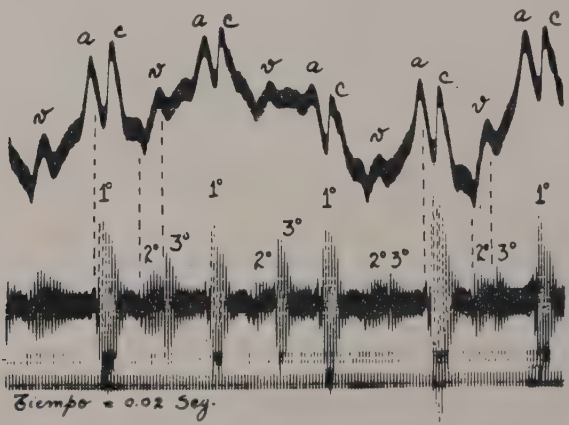


Fig. 137.—Records of heart sounds (lower) and jugular pulse (upper). A marked third sound is present. Its intensity varies and is greatest just after inspiration. Inspiration is indicated by a lowering of the general level of the venous pulse curve. (After Battro, Braun Menéndez and Orias: J. de Physiol. et de Pathol. Gen. 33: 51, 1935.)

in animals with an open chest by recording directly from the aorta. Wiggers and Dean[317] found that the first sound so recorded shows no preliminary vibrations, and is of somewhat higher pitch than that recorded from the ventricle. The sound is marked in the early stages of ejection when flow is rapid, may show a later exaggeration, but usually fades away before the end of systole.

That sounds develop in the muscle itself is definitely established, for sounds may be recorded from the beating excised and unfilled heart[167] and sounds may also be recorded from contracting skeletal muscle.[99]

The Second Heart Sound.—The second heart sound is developed from the closure of the aortic and pulmonary semilunar valves, and the vibrations that result are usually of a higher pitch than those of the first sound, namely about 50 to 70 a second. The two valves do not always close at exactly the same time, for asynchronism of the two ventricles has been described[191] and this may cause reduplication of the second sound. The closure of the valves occurs at that point in the disappearance of ventricular systole, when the pressures in the vessels exceed those in the ventricles, and varies, therefore, with vascular conditions. The second sound normally occurs slightly after the end of the T-wave. When conditions are altered, e.g., by adrenalin injection, it may considerably precede that wave. For some reason (unanalyzed) it usually precedes the end of the T-wave after meals, even though no marked change in blood pressure has occurred.

The Third Heart Sound.—The third heart sound may often be recorded, rarely heard. It develops some 0.1 to 0.2 second after the second sound and is particularly in evidence when the blood flow is rapid (e.g., after exercise). It probably develops in relation to the rapid inflow of blood from the auricle into the ventricle. Records illustrating the presence or absence of this sound in normal individuals, and the increased intensity of the third sound that may accompany inspiration, are shown in Figs. 136 and 137. In these records jugular pulse curves are also shown (these will be discussed later).

The Intensity of the Heart Sounds.—The intensity of the heart sounds varies with the force of the heart's contraction and the tensions developed in the heart, aorta, and valves. The use of the heart sounds for judging the force of the heart's contraction has been suggested by Wiggers. The loudness of the second sound may certainly be used to estimate changes in the tension of the large vessels, for increase in pulmonary or aortic pressures intensifies the sound. The fact that pulmonary arterial pressure may be effective in this way in spite of its much lower absolute level, probably depends on a difference in the structure of the pulmonary artery.

Timing of the Mechanical Events of the Cardiac Cycle

It is obviously difficult to time accurately the occurrence of the mechanical changes in the human heart. The shutting of the aortic and pulmonary valves can be accurately timed by the second sound, though it is not always easy to time the shutting of one of these, if they close asynchronously. The possible occurrence of auricular elements in the first sound precludes its use to time with equal accuracy the start of ventricular contraction. The relation of the different phases of the cycle to one another may be determined from the jugular pulse curve (see Figs. 136 and 137), but the actual times cannot be so determined with any accuracy, since the delay due to transmission along the large veins is not constant.

The most obvious method would appear to be that of recording the apex beat, but in actual use records of the apex beat are very complex. The impulse at the apex depends on the hardening of the ventricle during the isometric phase of contraction, on the recoil of the heart to expulsion, on the forward movement of the apex as the aorta is distended, as well as on a rotation of the ventricles. As soon as the ventricles commence to expel blood, they diminish in volume, so that a tambour placed over the apex beat records an uncertain integration of thrust and volume changes, mixed in proportions which vary from experiment to experiment, and even, owing to respiratory changes, from beat to beat. Some of the various types of records

obtainable by optical means are described by Weitz[307] and by Frey.[132] Auricular contraction usually gives a slow positive wave and the start of ventricular contraction a much more sudden and abrupt one. Occasionally, however, as with heart sounds, the abrupt wave is really of auricular origin. The expulsion period is usually marked by a much more rapid and forcible movement, which leads to an abrupt upstroke if the tambour is to the left of the main thrust and to an abrupt downstroke if it is to the right of it. The closure of the semilunar valves with the second sound and the later filling of the ventricle can usually be recognized. Many apex beat records, however, are obtainable which are practically impossible to analyze except in the light of simultaneous E.C.G. or pulse records, and even then the interpretation of some may be controversial.

It was shown by Yandell Henderson[163] that the recoil of the heart with expulsion is able to move the whole body. Even when a subject is lying on an ordinary spring bed, a tambour placed on the top of his head may record a footward recoil movement as the blood is thrust upward into the aorta, and a headward recoil movement as the stream is diverted round the arch. But these movements seem to develop with considerable lag, and to be unsuitable for timing.

Dressler[95] has given a very detailed account of the chest movements during cardiac contraction. In the expulsion period the sternum is depressed. This sternal depression, coupled with some recoil phenomena, has been utilized for timing the heart contraction. If a tambour attached to a heavy stand or to the bed be pressed against the sternum, and be connected to an optically recording segment capsule, the onset of ventricular contraction is usually indicated (but often not very clearly) by a slight depression followed by a brisk rise, and expulsion clearly by a rapid depression of the sternum.[37] The second sound is also usually clearly recorded. Whether the changes depend mainly on left or on right ventricular events is uncertain. A typical record is shown in Fig. 162.

EFFECTS OF THE CARDIAC CYCLE ON THE VESSELS

During the period of ejection the pressure in the *aorta* is closely related to that in the left ventricle. The only differences then existing depend on (1) the slight loss of free energy in passage through the aortic orifice, (2) the different distribution of free energy into pressure and kinetic energy, and (3) the different time relations for fusion of the main pressure wave with reflections of this wave from the periphery. After closure of the semilunar valves the pressure changes in the aorta proceed independently of those in the ventricle (See Fig. 132). The closure of the valve produces rapid vibrations associated with the production of the second heart sound. These are known as after-vibrations; they are preceded by a sharp notch, the incisura, and are followed by a longer positive wave, the dicrotic. When the ventricle ceases to expel blood the moving column continues to move forward in the aorta due to its own momentum and so creates behind it an area of relatively lower pressure; this produces the incisura. The blood returns later to equalize the energy distribution and closes the valves, thus producing the after-vibrations. Reflection of this wave from the closed valves produces a centrally generated positive wave, the dicrotic.

The pressure changes in the auricle are transmitted to the *veins* and produce a pulse recordable in the jugular vein which is known as the *jugular or venous pulse*. This may be recorded in animals by direct connection of the jugular vein with a recording system. It may also be recorded in man without much difficulty. If a person lies down so that the veins of the neck are not emptied by gravity, there may be observed just above the clavicle a pulsation which is due to changes in pressure in the jugular vein. If an open cup connected to a light recording tambour be applied gently to this area, a record may be obtained of these pulsations.

The waves of the venous pulse (Figs. 136 and 137) correspond closely with those recordable within the auricle, except that the wave which is caused in the

auricle by the upward bulging of the tricuspid valve with ventricular systole is much exaggerated. This exaggeration is probably due to the addition of a new element to the auricular wave. There appear consequently three definite positive waves, conventionally labelled *a, c,* and *v*.

When the auricle contracts, the centripetal flow of blood in the large veins is temporarily impeded; possibly there is a slight reflux of blood. The pressure in the large veins is raised and the wave so produced is labeled *a*. When the tricuspid valve closes or bulges into the auricle at the start of ventricular contraction a similar wave of raised pressure is produced. If the veins are very congested, this may travel relatively rapidly up them and cause a second increase in pressure. Under more normal conditions of venous pressure it travels more slowly, and the pressure wave in the carotid artery (starting later because of the isometric period) reaches the extrathoracic vessels at about the same time. This arterial wave is transmitted not only from the carotid artery but also from the aorta and other large arteries to the large veins and a positive wave is thus created, which from its relation to the carotid pulse is called the *c* wave. This wave may, therefore, be derived from three sources: (1) from the carotid, (2)

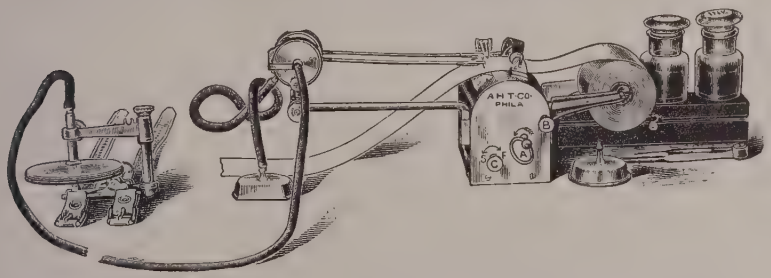


Fig. 138.—Polysphygmograph. This instrument records in ink on glazed paper two simultaneous tracings, i. e., radial pulse and one other, such as carotid, jugular, apex beat, etc., in addition to the time tracing.

from the aortic pulse affecting the large veins at the heart, (3) from a true venous wave. During the early part of ventricular expulsion the stretching action of the downward movement of the base of the heart lowers the pressures in the auricle and large veins. This gives a negative wave. As the incoming blood stagnates during ventricular systole the auricle and veins fill and raise the pressure, while the return of the base of the heart, as recoil ceases, creates another positive wave. Together these form the *v* wave. Finally, the auriculoventricular valves open and the venous pressure again falls as the ventricle fills. The waves of the venous pulse may be compared also in point of time with arterial pulse tracings from the brachial or radial. As a result of the time taken for the transmission of the arterial pulse to the arm, the part of the venous pulse which corresponds with it is recorded in the neck about 0.1 second earlier. An ink recording "polysphygmograph" is shown in Fig. 138 and a typical normal record obtained by this instrument in Fig. 139. The relation of the venous waves to those in the auricle may be seen by comparison with Fig. 132.

In taking a record with a polysphygmograph the levers cannot be exactly aligned. At the end of a record the paper must be stopped and the levers allowed to draw their arcs on the stationary paper, as at *X* in Fig. 139. Any given distance measured back from these

arcs represents comparable points in time. For instance, 9 mm. back on the upper jugular pulse record is at the start of a *c*-wave; a similar distance on the radial pulse falls ½ of 1 time division (or 0.1 second) ahead of the radial upstroke. These two waves, therefore, represent ventricular systole. The a-c interval indicates the transmission time from auricle to ventricle, and like the comparable P-R interval of the E.C.G. should rarely exceed 0.2 sec. The c-v interval is, normally, about twice the duration of a-c. Examples of waves optically recorded have been given in Figs. 136 and 137, where the relation of the v-wave to the end of systole is more definitely shown. The double origin of the v-wave is often shown by a duplication of this wave (though not in the examples given). The possible double origin of the c-wave is rarely shown in a duplication of this wave except sometimes accompanying marked venous engorgement. When the pulse is slow an additional positive wave is sometimes seen between *v* and *a;* it corresponds with filling of the auricle and the so-called period of diastasis. Some indications of it may be seen in occasional pulse cycles in Fig. 139.

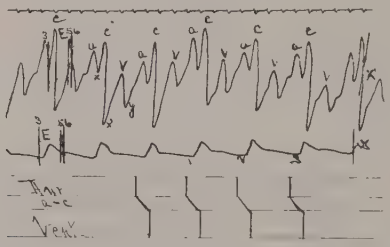


Fig. 139.—Normal jugular tracing. The spacing below shows the duration of the *a*-*c* interval. (From Carter.)

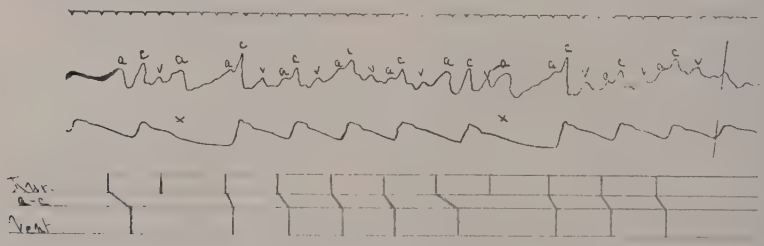


Fig. 140.—Dropped beats. Second stage of heart block. (From Carter.)

The delayed conduction from auricle to ventricle, the occasional missing of conduction, and the improvement in the rate of conduction after the consequent rest may all be demonstrated in cases of partial heart block by comparison of jugular and arterial pulse curves. One such record is shown in Fig. 140, where one pulse in six fails to be conducted. The start of auricular contraction and the *a*-*c* interval are shown diagrammatically below the actual record, and demonstrate very clearly how conduction rate is slowed just before it fails altogether. The polysphygmograph used in the simultaneous recording of these pulses had at one time a considerable clinical usefulness, but with the development of portable electrocardiographs, it has largely disappeared from the equipment of the clinician.

CALCULATION OF THE WORK OF THE HEART

The heart burns foodstuffs and utilizes oxygen and thus makes energy available for doing work. The efficiency of the heart, like that of other muscles, is such that some three-fourths of the energy becomes heat and one-fourth or less may be used to do mechanical work. Even this one-fourth ultimately be-

comes heat through friction in the vessels. The work done by the heart in contraction (systole) is expended entirely in raising the pressure within its chambers, and the energy made available is entirely pressure energy. But the work so performed raises the free energy above that in the large arteries, so that blood flows out into the aorta with little frictional loss. As the total energy may be considered the same, it becomes simpler to estimate the work done by the heart from the energy changes in the aorta than from those in the heart itself. In the aorta, part of the energy is present as pressure, for the heart forces fluid out into the aorta, where it raises the pressure and stretches the walls of the vessel; the work necessary to accomplish this may be measured by the volume of blood moved and the pressure to which it is raised. A much smaller part of the work done is utilized in developing kinetic energy.

The total work done in developing pressure energy, is p V where V is the volume moved and p the pressure developed. If the lateral pressure in the aorta during the systolic period when blood is flowing into it be assumed to be 90 mm. Hg (122 cm. pressure of water or 122 grams per sq. cm.) and if the volume of blood expelled per beat be 60 ml., then the total work done in developing *pressure energy* (p V) in the aorta is approximately 122×60 or 7320 gram-centimeters.

Since pressure energy can readily be changed into kinetic energy with little loss, and the reverse change can also occur (but with greater loss of free energy) measurements of pressure and velocity energy should be made at the same section of the system; in published experimental work this essential principle has not always been followed. If the output of the heart be assumed as before, and if the pulse rate be 65, the systolic expulsion period is likely to be about 0.32 second. If the cross-sectional area of the aorta be 2.7 sq. cm., the mean *systolic* velocity (v) must be 69.4 cm. per sec. (the estimate made by Stephen Hales in 1733 was 74 cm.). The work done developing kinetic energy per milliliter is $\frac{v^2W}{2g}$, its total for an output of 60 ml. or 63 Gm. (if the density, W, is 1.05) is approximately 155 gram-centimeters or only 2.1 per cent of the total work. The figures that have been given represent probable values for man under basal conditions when the circulation is minimal. During activity, and especially during exercise, the work performed by the left ventricle of the heart must be much greater, and the increase must be especially marked in the kinetic energy factor since this will increase with the square of the velocity. During muscular work it is probable that development of kinetic energy may often amount to 20 per cent or more of the total work of the left ventricle. Energy exchanges from changes in position energy may be considered negligible as far as the relation of the left ventricle to the aorta is concerned, when the subject is lying down.

The pulmonary system will be considered later, but it may be pointed out here that inasmuch as the pressures developed in the pulmonary artery are much lower, while the velocities are of the same order as those in the aorta, the relative importance of kinetic energy is much greater.

The total work done by each ventricle per beat is expressed approximately by the sum of $p\ V + \frac{Mv^2}{2g}$, where p is the mean pressure in the aorta or pulmonary artery during the period of expulsion, V the volume and M the mass of blood expelled, and where v is the mean velocity of the blood in the aorta or pulmonary artery during expulsion. As will be seen later, the diameter of the aorta increases with age, and, consequently, for similar stroke volumes the velocities developed are reduced. Kinetic energy plays a smaller part in the work of the heart in older individuals. The values calculated are inaccurate. If it were possible, integration of the curves representing expulsion should be used. Without such integration the estimates of kinetic energy are too low.

The true elasticity of vessels, by virtue of which they are capable of performing during rebound almost as much work as was expended in the original stretch, is very great. Fleisch[118] found a loss of work of only 1 per cent in the aortic arch, 2 per cent in the ascending aorta, 7 per cent in the abdominal aorta, and 13 per cent in the femoral artery.

VARIATIONS IN CARDIAC OUTPUT

The factors causing variations in cardiac output are the properties of heart muscle already considered, particularly the effect of venous filling and the modifications induced by nervous and chemical influences acting on the heart. The effect of the properties of heart muscle itself may be distinguished from the others most readily in experiments on the isolated heart-lung preparation which was developed by Starling and his associates and in which many of the complexities of the circulation in an intact animal are absent.

The Isolated Heart-Lung Preparation

The fact that even a mammalian heart can continue to beat for hours after removal from the body, if kept warm and supplied with an oxygenated salt solution in which the electrolytes are properly balanced, has already been mentioned (page 348). Such a heart is, however, far from normal and is incapable of obtaining from the solution enough oxygen to perform any extensive work. If, however, the heart be supplied with blood, conditions are much more nearly normal. The simplest method of oxygenating the blood is to utilize the animal's own lungs, though a mechanical oxygenator can be used,[89] should the use of the lungs be undesirable.

The arrangement for the perfusion of the heart and lungs, which was devised for this purpose by Knowlton and Starling, is shown in Fig. 141. The blood is prevented from clotting by hirudin or heparin, or defibrinated blood may be used. The blood is discharged from the left ventricle into a cannula connected with the innominate artery and all the other branches of the aorta are tied. A side tube, *V*, connects with an air cushion, *B*, to give the necessary distensibility to the "arterial" system; the peripheral resistance, *R*, is formed of thin rubber tubing compressed by an adjustable air pressure. It should be noted that such a resistance, while convenient to use, is very different from that of a normal vascular system, for it forms an absolute obstruction when the arterial pressure falls below that in the air chamber. On the other hand, when the arterial pressure is raised considerably, the tube can open widely and offer a very low resistance. From *R* the blood flows to a syphoning system, *Sy. N*, which serves to measure the volume of the cardiac output directly. It then passes to a reservoir, *F*, where it is warmed, and from there goes to the right auricle. The pulmonary artery conducts it to the lungs, where it is oxygenated through artificial ventilation, and the pulmonary veins conduct the oxygenated blood to the left auricle. All the blood ejected by the left ventricle passes through this artificial circuit except that which enters the coronary arteries. Pressures may be recorded from the right auricle (*I V C*) and from the aorta (*C A*). The pressures in the pulmonary circuit may also be recorded.

Measurements of the volume changes in the ventricle may also be made by enclosing the ventricles in an air-tight chamber. Such a condition can be approximated by utilizing a glass funnel covered by a rubber membrane. A hole is cut in the rubber so that it fits tightly, but not too tightly, around the auriculo-ventricular groove. The ventricles are slipped through the hole so that they lie in the closed space of the funnel. The only exit is provided by the tubular end of the funnel which is connected to an air-tight mechanically, or optically, recording tambour. Any reduction in the volume of the ventricles lowers the pressure within the system and causes the tambour to be sucked in. The tambour may be calibrated so as to allow quantitative measurements of the changes in volume. This method is not only useful in analyzing cardiac events with the isolated heart-lung but also with the exposed intact heart. Such a closed system enveloping the heart is called a cardiometer or heart-plethysmograph. The volume at the end of diastole (diastolic volume) represents that of the filled heart. The volume at the end of systole (systolic volume) is the volume attained after expulsion of blood. The heart is normally only incompletely emptied. The difference between these two volumes represents the sum of the stroke-volumes of the two ventricles.

The Effect of Varying Venous Inflow.—Variations in the rate of venous filling and the pressures at which the auricle and ventricle are distended in diastole (and consequently their diastolic volumes), may be attained in the heart-lung preparation by varying the height of the reservoir *F* (Fig. 141). If this be raised, the pressure at which the right heart is filled is increased. With a greater diastolic volume the heart contracts more forcibly, discharges more blood into the pulmonary artery, and the blood returned by the pulmonary veins is increased. A similar process then follows in the left heart chambers. The

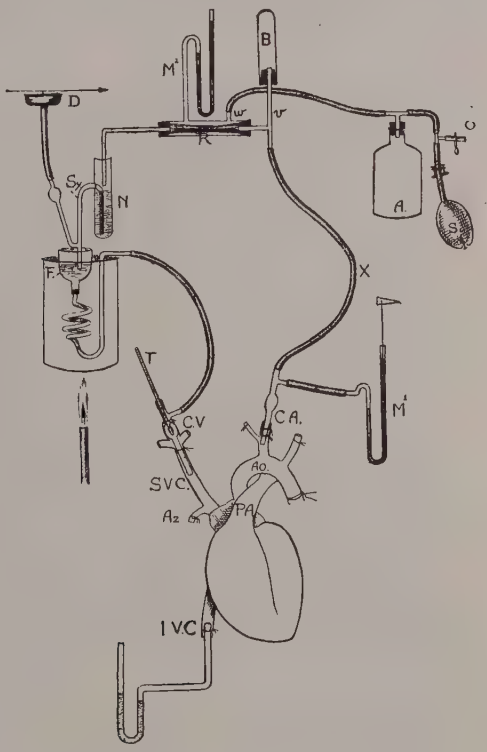


Fig. 141.—Arrangement of apparatus for heart-lung preparation of mammalian heart. (Knowlton and Starling.[203])

effect of increasing the right auricular pressure from 9.5 to 14.5 cm. of water, and then lowering it to 5.5 cm. is shown in Fig. 142. The pulse rate was 132, and in period *A* the stroke volume for each ventricle was 5.7 ml. The dog was one of 5 kilos weight. In this period *A* the minute volume was, therefore, 752 ml. (somewhat above a basal value), the pulse rate high, and the stroke volume subnormal. In period *B* when the venous inflow was increased, the heart at first was unable to eject all the entering blood, and the residue so left in the incompletely emptied ventricle added to the newly entered blood, increased the diastolic volume. As a result of this increase the heart became able to eject all

the entering blood, though at the cost of less complete emptying. This reaction is shown in Fig. 142 in the heart plethysmograph or cardiometer record (upstroke indicates contraction). It may be noted that for a while the cardiac systolic volume (volume at completion of systole) exceeded the previous diastolic volume; then the slight increase in arterial pressure assisted the coronary circulation sufficiently to allow some improvement in cardiac efficiency; there resulted a partial return towards the previous cardiac volume, in spite of the maintenance of a high output. In this phase the stroke volume was 8 ml. per beat and the minute volume 1056 ml. (values which are above the normal basal level). With the final reduction (in stage *C*) in venous inflow to values definitely subnormal

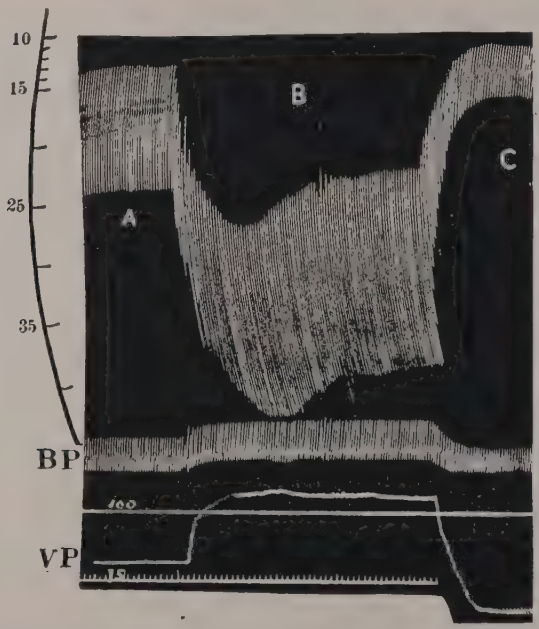


Fig. 142.—Isolated heart-lung preparation. From above downwards: cardiometer record (upstroke is contraction); mean arterial pressure (*BP*); venous pressure (*VP*); and time in seconds. The line 100 indicates the 100 mm. of water level for venous pressure. The scale to the left gives the graduations of the cardiometer (volume change for the two ventricles). When *VP* is suddenly increased, cardiac volume increases, and cardiac contractions become more forcible, but at first the heart output does not keep pace with the inflow. *A*, *B*, and *C* indicate the three stages discussed in the text. (From Patterson, Piper, and Starling.[241])

not only for minute but also for stroke volume (stroke of 2.5 ml. and minute volume of 330), the adjustments were reversed. The main change in cardiac output in *B* and *C* was attained by utilizing the effects of increased or decreased initial stretch. The more gradual changes (as the result of which in period *B* the heart was enabled to do the adequate work without utilizing such a large proportion of its reserve capacity) probably depended on an improved chemical condition through a more adequate supply of oxygen. It should be emphasized, however, that the peculiar characteristics of the artificial resistance used in the heart-lung preparation allowed an increase in cardiac output of 40 per cent

with an increase in the mean arterial pressure of only 5 per cent (124 to 130 mm. Hg), so that the consequent increase in coronary blood flow to which these secondary effects must be ascribed must have been slight.

The Effects of Varying Peripheral Resistance.—If the inflow, and consequently the outflow, be kept unchanged, the work the heart has to do is greatly altered by a change in peripheral resistance. Yet these demands are readily met, if they are not too extreme. The mechanism involved in overcoming an increased resistance is the same as in the previous case. Residual blood, left as the result of incomplete emptying, can increase the diastolic volume. An example is shown in Fig. 143 which was obtained in the same animal as was Fig. 142. In the initial stages conditions were similar to those in Stage *A* of that figure, except that the

Fig. 143.—Record similar to that of Fig. 142, but showing the effects of increased peripheral resistance (indicated by rise in B.P.). Note that incomplete emptying against increased resistance increases diastolic volume and venous pressure, that diastolic volume and venous pressure fall again as improved coronary circulation assists the heart, that strict proportions between venous pressure and ventricular volume do not obtain. (Patterson, Piper, and Starling.)

mean arterial pressure was only 68 mm. This was raised to 128, then lowered to 75. The increased residual blood and increase in diastolic volume indicated in the cardiometer record of Fig. 143, necessitated the damming back of blood in the reservoir *F*, and a consequent rise in venous pressure. On return to a lower arterial pressure, and poorer coronary blood supply, the somewhat fatigued heart showed a progressive slow dilatation.

The effects on diastolic volume of *increased venous filling and increased arterial resistance* acting together may be additive, but need not necessarily be so. The effects of increased arterial resistance depend on the damming back of blood and a consequent rise in venous pressure, and cannot therefore be effective, if the conditions prevent any such rise, or if

venous pressure and diastolic filling be increased beyond the optimal values. Consequently the effects may be complex when both factors are varied together, particularly if the pulse rate is changed at the same time. The interdependence of these factors has been partly analyzed on the perfused turtle heart.[242] The importance of the regulation of cardiac rhythm as a supplementary control in the intact animal is thereby demonstrated.

The Effect of Changes in Pulse Rate.—The primary effects of changes in the pulse rate on the condition of heart muscle may also be analyzed in the heart-lung preparation by causing changes through electrical stimulation of the cut vagi or sympathetic nerves or by changing the temperature. Under such conditions the effects produced are determined to a large extent by the adequacy of venous filling, for if the pulse rate is increased there is a tendency (unless the venous reservoir is raised) for the heart to be filled incompletely and for the stroke volume to be diminished. Stimulation of the accelerators therefore increases the minute volume, but reduces the level of blood in the reservoir and decreases diastolic filling. Thus in spite of a more forcible heartbeat the stroke volume is decreased and the increase in minute volume is slight. Only if the venous pressure is also raised is the stroke volume maintained. Similarly, vagal stimulation, which slows the heart and lengthens diastole, decreases the cardiac output and allows the level in the venous reservoir to rise. The improved diastolic filling later results in an increased stroke volume which compensates to some extent for the slow pulse rate.

In the intact animal with venous return at a normal level a moderate increase in pulse rate shortens diastole in the period of diastasis (see page 378) and so interferes little with the filling of the heart; there may be little reduction in stroke volume. If the change in rate is greater, the more active period of filling may be shortened and stroke volume may therefore be reduced. It is apparent that with an increase in pulse rate cardiac output per minute may be increased, remain unchanged, or even be reduced, depending on the balance between rate and level of venous return.

The Effect of Temperature Changes on the Heart.—This may be demonstrated on the isolated frog, turtle,[242] or mammalian heart, in the heart-lung preparation and in the intact animal. There is a very definite increase in pulse rate with increase in temperature, but the relationship is neither a simple linear nor a logarithmic one.[67] Sometimes sudden changes in rate may occur at a certain temperature level. Such changes have been ascribed by Crozier and his associates (for review see Barcroft[21]) to the interaction of two or more processes with different temperature coefficients. Doubt has been thrown on the adequacy of this conception (Burton[58]).

In the frog heart a rise of temperature produces a more forcible contraction if the rate is kept constant. When the frequency is allowed to rise, the force is diminished. The optimal fiber length for development of tension is increased (Fig. 104). Conduction from the auricle to the ventricle is accelerated and the duration of the electrical changes accompanying contraction is reduced. The processes of relaxation are also accelerated. In the heart-lung preparation warming the inflowing blood increases the frequency of contraction; if the venous inflow is kept constant (reservoir level unchanged) there is no change in the flow per minute. The reduced duration of diastole causes a poorer attainment of equilibrium during filling, so that the discrepancies between the observed diastolic pressures in the right heart and those theoretically attainable are greater. The diastolic filling is less complete, and the *law of the heart* results in a small stroke volume. The opposite effect is seen with cooling. There appears, however, to be an additional effect, for the cooled heart beating slowly empties itself more effectively than does the warmed rapidly-beating heart. Under conditions of inflow adjusted so that the diastolic volumes of the cooled and warmed heart are the same, the systolic volume of the cooled heart is smaller and the stroke volume greater. The duration of systole

in the cooled heart is also longer than that normally observed at slow pulse rates obtained by other means. The dog's heart can contract at temperatures between 26° and 44° C., but near the limit of these ranges, it may begin to fail, and the output may be reduced. Such failure is accompanied by sudden acute dilatation. The oxygen consumption of the heart is greater at the higher temperatures.

Chemical Effects on the Isolated Heart.—Chemical effects on the heart may be demonstrated in the heart-lung preparation either by the addition of substances to the blood in the venous reservoir, or by altering the gases used to ventilate the lung. *Adrenalin* added to the reservoir produces a great increase in the pulse rate. With the shortening of diastole the heart is incompletely filled and diastolic volume is reduced. In spite of this decreased initial stretch the efficiency of contraction is maintained, or even improved, and the systolic volume of the heart is also reduced. The stroke volume (difference between diastolic and systolic volumes) is usually slightly increased but may be decreased. The cardiac output per minute is usually only slightly increased. The reduction in diastolic filling is apparently not due entirely to the shortening of diastole with the change in pulse rate. If the concentration of CO_2 in the air used for ventilating the lungs is greatly increased at the same time that adrenalin is added to the circulating blood, the increase in pulse rate is maintained, but the reduction in diastolic filling no longer develops. The CO_2 exerts a dilating effect so that filling is improved without losing the more effective emptying produced by adrenalin. Both the stroke volume and pulse rate are therefore increased, and cardiac output per minute is raised considerably. The combined effect is not predictable from the effects of the two agents acting separately.[245] Adrenalin under these conditions acts as though the optimal pH for cardiac activity had been lowered.

Excess of CO_2 and lack of O_2 acting in the absence of adrenalin produce a dilatation of the heart with increase in diastolic volume. Emptying is also less effective so that systolic volume is also increased. Stroke volume may increase slightly or decrease (usually there is an increase initially with CO_2 excess but not with lack of O_2).

Cardiac Filling in Hearts With Valvular Lesions

The main factor concerned in compensation is Starling's law of the heart. The leaking valves allow filling to be exaggerated by the addition of regurgitating "pendulum" blood. The consequent increase in the initial stretch causes the heart to contract more forcibly.

Aortic Regurgitation.—The primary effects are relatively simple. During ventricular diastole blood regurgitates from the aorta into the ventricle; the amount depends on the size of the hole, the difference in pressure, and the duration of diastole. Regurgitation occurs throughout diastole, but especially in the earlier phases when the arterial pressure is high, and ventricular pressure low. Measurements of intraventricular pressure in experimental animals with aortic regurgitation do not show any considerable diastolic rise above the normal; the heart appears to be sufficiently distensible to accommodate the increased volume with only a moderate increase in pressure. Consequently, the discharge of blood from the left auricle can also continue normally, with only a moderate rise in pressure in the pulmonary veins, and dilatation of the left auricle. The two inflowing streams interfere only slightly with one another. The regurgitated blood is thus added to the normal volume, and the increased filling enables the heart to contract more forcibly and so expel both its normal output and the "pendulum" blood.

The left ventricle is dilated, though the tendency to dilate is diminished by a reflex increase in pulse rate and the shortening of diastole.[38, 111] The latter decreases the blood added

to the ventricle per beat from the auricle, as well as that regurgitated. It is important to recognize that under these mechanical conditions the dilatation may be limited in a healthy heart to one chamber. An increase in pulse rate may so mask the effect by causing a reduction in the filling of the right ventricle that the dilatation may not be recognizable in x-ray shadows except as a change in the shape of the heart.

Mitral Regurgitation and Stenosis.—Regurgitation through the mitral valve is more serious mechanically than regurgitation through the aortic valves, since it is a systolic and not a diastolic event. The mechanical efficiency of the heart's contraction is interfered with[195] and, as Wiggers[315] has so excellently emphasized, a slowly contracting heart may empty all its blood into the auricle, where the pressure is low, and none into the aorta where the pressure is higher. Actually the heart contracts rapidly, the regurgitation is inadequate to carry the whole volume, and blood is also forced into the aorta. A considerable volume may, however, regurgitate and temporarily raise the pressure both in the auricle and in the pulmonary veins. The consequent dilatation of the auricle assists auricular contraction, so that it is able to empty into the ventricle both its normal contribution and the "pendulum" blood, and in turn the increased filling of the ventricle assists it to perform the additional work. In this way the pressure in the pulmonary veins is probably reduced to normal values after auricular contraction, so that a normal outflow from the pulmonary veins into the heart can be maintained with only minor and temporary increases in venous pressure. This rise in venous pressure does, however, increase the tendency to pulmonary congestion. The ventricle has to do more work, but the pressure supplying the coronary arteries is not raised.

The real danger is that the slower the muscular contraction the greater the regurgitation; hence any enfeeblement of cardiac action tends to start a vicious circle. As Wiggers[315] has pointed out, "mitral insufficiency is dangerous not by virtue of the circulatory changes induced, but on account of the constant liability that decompensation may result from any cause which weakens the ventricular contraction."

Disease of the mitral valve may lead to fibrosis with narrowing of the orifice. This is known as stenosis. The conditions in the heart involve principles similar to those concerned in regurgitation. Usually some regurgitation accompanies stenosis. The narrowing of the orifice hinders the filling of the left ventricle. Residual blood in the left auricle dilates the chamber and raises the pressure within it. The resulting stretch of the muscle fibers improves the capacity of the left auricle to contract and so leads to compensation. The left auricular muscle fibers become larger and thicker. Hypertrophy of the muscle develops. Such compensations, however, fail to relieve the raised pressure in the left auricle, with a consequent rise in pressure in the pulmonary veins. Pressures consequently tend to rise in the pulmonary vessels and pulmonary edema becomes a complicating factor. At the same time the interference with the filling of the left ventricle makes it difficult for the initial tension in this chamber to rise even to normal levels. It is consequently difficult for the left ventricle to utilize its normal mechanisms of compensation.

Efficiency of Cardiac Contraction

The heart-lung preparation may be used in investigating the oxygen consumption of the heart and the mechanical efficiency of contraction. Variations of the diastolic length of the fibers brought about by alterations of inflow or arterial resistance enable the heart to perform varying amounts of work. When the muscle remains in good condition the work performed is directly proportional to the diastolic volume, and the efficiency of the heart is of the order of 20 to 30 per cent. Efficiency of a muscle is expressed by the ratio of work done to total energy output. The latter may be determined by the amount of oxygen used (see page 772). The methods used to calculate the work done by the heart have been described (page 386). When the condition of the heart is impaired, for example, by high tensions of CO_2, anoxemia, chloroform, excess load, or absence of insulin in the perfusing blood, the efficiency of the contraction is reduced, but the metabolic level (as indicated by oxygen consumption) is still directly determined by the diastolic volume.[287] This fact is shown in Fig. 144. Curve 1 describes an experiment in which the heart was in good

condition, and the diastolic volume varied with the load. The relationship between oxygen consumption and diastolic volume was linear; the mechanical efficiency was relatively constant. On the other hand, in the experiment which yielded curve 2 the load and the work performed were maintained constant, yet the condition of the heart deteriorated, and its diastolic volume continually increased. The oxygen consumption varied directly with diastolic volume, but showed no relationship to the work performed. The efficiency of contraction decreased steadily. In the experiment of curve 3 both the load imposed on the heart and the efficiency of its contraction varied, but again diastolic volume and oxygen consumption showed a linear relationship.

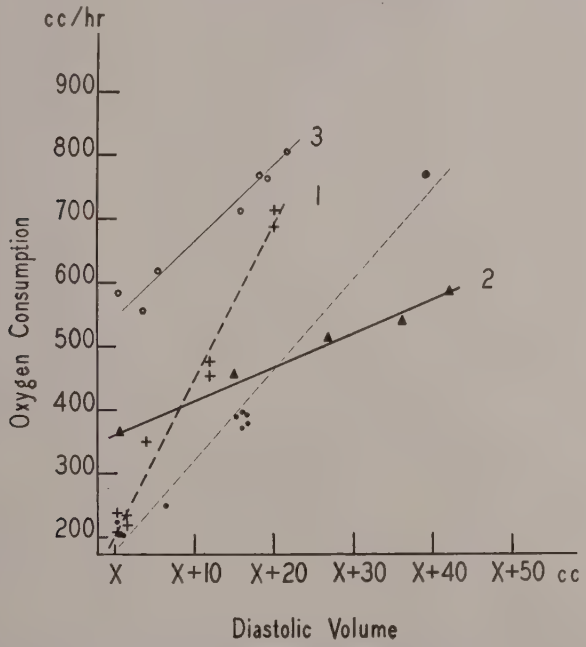


Fig. 144.—Relation of oxygen consumption to diastolic volume in four experiments. The conditions giving curves 1 to 3 are described in the text. The other line represents an additional experiment of the same type as that of 3. (From data reported by Starling and Visscher: J. Physiol. 62: 243, 1927.)

Impairment of the heart's condition is indicated by a low mechanical efficiency. This results in retention of blood through ineffective emptying and increased diastolic volume. The heart retains its capacity to perform the required work but does so at the cost of a raised metabolism and utilization of some of its reserve power. If the oxygen requirement becomes very great, the coronary blood supply may be inadequate to maintain a normal condition of the muscle, and anoxemic dilatation may be added to that previously present; it may lead to rapidly progressing heart failure. If the coronary circulation is adequate, the additional work induced by increased output or arterial resistance may be met by an initial dilatation which subsides somewhat as the increased

arterial pressure further improves the coronary circulation, and so increases the mechanical efficiency. This may be noted in Figs. 142 and 143. The importance of adjustment of heart size to the work to be performed is indicated by the data of Starr and his associates,[288] who found clinically that damaged hearts have a diastolic volume abnormally great for the amount of work performed (see Fig. 145). Such an enlargement is considered strong evidence of myocardial disease and weakness.

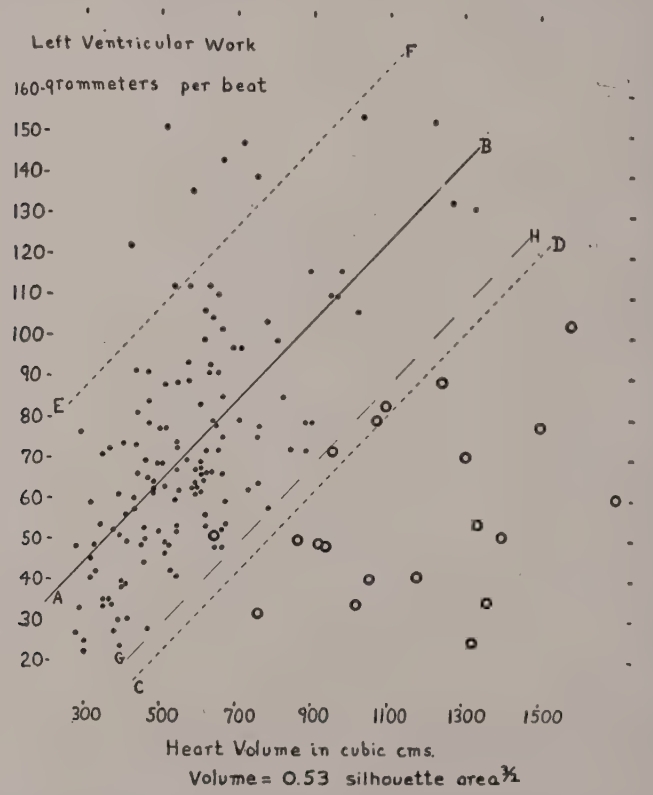


Fig. 145.—The size of the heart (abscissae) plotted against the estimated work of the left ventricle per beat (ordinates). The open circles represent those cases which had shown symptoms of decompensation at an earlier date. (From Starr et al.: J. Clin. Invest. 13: 561. 1934.)

Cardiac Compensation.—A strain is thrown on the heart when the work it has to perform is increased, whether this result from an inadequate valvular action or from an increased peripheral resistance. The strain may also result from disease of the heart which weakens the force of the muscular pump, and renders it inadequate to accomplish readily a normal amount of work. When compensatory mechanisms allow such a strain to be met without cardiac failure, though with the loss of some reserve power, the condition is said to be compensated. Compensation is achieved through two normal mechanisms, dilatation and hypertrophy. The former utilizes the reserve force derived from the increased initial stretch in diastole which accompanies a simple increase in venous return or the addition to the

venous inflow of blood left by an incomplete emptying of the ventricle in the previous contraction. Hypertrophy develops as the result of the capacity of all muscle fibers to grow in length and thickness when constantly submitted to increased loads. This growth is thought to be dependent on the increased blood supply to a muscle that follows a period of increased work. Consequently, cardiac hypertrophy may be difficult to attain when the strain is associated with a coronary flow which is inadequate for the metabolism of the heart. This is the case whether the depressed flow depends on actual disease of the coronary vessels, or on an inadequate arterial pressure. Both methods of compensation are accompanied by reflex changes in the pulse rate, which depend on the interactions of responses to changes in both arterial and venous pressures; the net effect of such reflexes is usually to produce a more rapid rhythm, but this is not invariably the case. Valvular lesions necessitate the same sort of adjustments, but certain factors are exaggerated.

The *dilated heart* is one whose size is increased out of proportion to the work performed, and which is utilizing, even under basal conditions, some of its reserve force. This may be seen in Fig. 145, where hearts of individuals with a history of decompensation (though for the time being they were compensated) are seen to have a large size relative to the work performed; they fall quite definitely outside the broad limits of variability seen in more normal subjects. This dilatation is attained through a raised venous pressure.

In some chronic cardiac conditions the heart may be large and apparently dilated with only minor increases in pressure in the systemic veins. Here the dilatation may be mainly on the left side, and affect the pulmonary veins where it cannot be measured, or perhaps asphyxial products resulting from a poor coronary supply may modify the elastic constants of the heart, so that dilatation occurs at a lower pressure. To some extent, however, apparent discrepancies probably depend on the chronic character of the disease, on the consequent gradual stretching of the pericardium, and on the existence of an abnormally large heart (dilatation following hypertrophy). In a spherical organ the initial tension, and consequently the lengthening, produced in any given muscle fiber for any given increase in internal pressure is greater the larger the cavity. Since it is probably the initial lengthening of the muscle fiber that is important in effecting compensation, a small rise in venous pressure may then be able to induce a considerable effect.

The *hypertrophied heart* is one whose size is large, but in which the increase in size is not out of proportion to the work performed. The increase in size here depends on increased muscular tissue. Such hearts fall within the normal limits of a graph such as that of Fig. 145. The cavities may be large, but the venous pressure is not raised, and the reserve force obtainable from initial stretch is not prematurely exhausted.

Differentiation between dilatation and hypertrophy is not readily attained, since commonly both conditions are present. In the hypertrophied heart the Q-T interval in the electrocardiograph is usually somewhat long; the lengthening is mainly in the QRS complex, and may depend on the greater distance the excitatory wave has to travel. The venous pressure should be within normal limits, if simple hypertrophy is present. In the dilated heart the Q-T interval is often also lengthened but the lengthening is mainly in the S-T interval.

The duration of systole and of the Q-T interval in the E.C.G. vary with the pulse rate, and are affected also by other factors, such as vagal and sympathetic activity or the influence of adrenalin. Therefore these times are useful clinically only when they vary considerably from the normal, as indeed they often do. The normal standards are useful even if inexact.

In normal males with the subject lying down the values of the Q-T interval, expressed in seconds, are found to average for a pulse rate of 60, 0.400, for one of 80, 0.361, and for a rate of 100, 0.338; in female subjects the times are somewhat longer. They equal 0.1536 cycle + 0.2462 for males and 0.1259 cycle + 0.2789 for females.[2] For wider pulse rate ranges, including the normal rapid rates in children and the slow pulse rates of athletes, the Q-T interval may be better represented as equal to $0.37\ \sqrt{\text{cycle}}$ for males and $0.40\ \sqrt{\text{cycle}}$ for females when the subjects are sitting.[31] With the subjects lying down the durations are somewhat longer, and the values of these latter constants may be increased by about 0.03.

Cardiac Tone.—The term *cardiac tone* has been used in many ways. In muscle physiology tone is used to describe a maintained postural contraction which is neurogenic. In the case of a hollow viscus tone is the adaptation of the size of the viscus to its contents. The stomach, for instance, can adjust itself to its contents in such a way that the volume contained may vary enormously with only slight changes in intragastric pressure. There is no evidence that tone, in this sense of the word, is present in the mammalian heart. The

statement has been made that CO_2 favors dilatation; this implies that the diastolic coefficient of elasticity may vary and that the diastolic volume of the heart is not determined simply by the distending pressure. There is not conclusive evidence of the presence of such additional factors.[237] Under most conditions diastolic volume and venous pressure vary together, and the discrepancies may be due to opposed changes in the right and left hearts. Clinical cardiac dilatation not associated with raised venous pressure may, for instance, depend on left cardiac failure and raised pressure in the pulmonary veins. However, the data of Starling[240] as well as the more recent and detailed data of Johnson and Katz[189] do suggest that changes in the volume elasticity coefficients of the heart in diastole may accompany changes in efficiency. The latter workers suggest that a decreased "tone" may be beneficial in a failing heart.

Importance of the Pericardium.—Kuno[207] used the heart-lung preparation to test the effect of the pericardium. He found that after its removal diastolic volume may be greater at any given venous pressure. He considered that this structure is a factor which prevents acute overdilatation. It has been shown by x-ray studies that while an animal (or man) may continue to lead a normal life after removal of the pericardium, the diastolic volume is often large, and the heart may dilate abnormally in response to an experimental plethora (for literature see Carleton[64]). The heart may dilate considerably even when the pericardium is intact. Although the pericardium may stretch to some extent it doubtless limits dilatation. If tension is maintained continuously as in pericardial effusion or when a heart hypertrophies, the pericardium certainly stretches considerably.

Any acute collection of fluid in the pericardium, whether produced experimentally, or by disease, or as the result of hemorrhage into the pericardium from injury of the heart, serves to illustrate the importance of filling for effective cardiac action. Raising the pressure within the pericardium and so interfering with venous return raises venous pressure. Even so, owing to the resistance of the pericardium to any acute stretch, the increase in venous pressure may be unable to force blood into the heart. Cardiac filling is inadequate or may fall to zero and the circulation rapidly fails.

CARDIAC OUTPUT IN THE INTACT ANIMAL

The factors concerned in the intact animal are those already considered, but conditions are complicated by various adjustments produced by reflex or hormonal changes. The factors concerned are expressed diagrammatically in Fig. 146. Further details of reflex adjustments will be given later.

Measurement of Cardiac Output in the Intact Animal

The methods of measurement so far discussed are crude and obviously applicable only under very abnormal conditions. Much effort has consequently been directed to measurements of cardiac output in the intact animal and in man. Most of these depend on deduction from the respiratory exchange according to the principle first enunciated by Fick.[115] The lungs cannot store, except temporarily, any considerable volume of blood, so that normally the output of the left and right ventricles must be identical. In its passage through the lung the blood from the right ventricle takes up O_2 and gives off CO_2 and the extent of this gas exchange must obviously be dependent on the available blood. To illustrate this by a concrete example, let us suppose that the oxygen consumption of an individual is 220 ml. per minute, that the venous blood enters the lung with 145 ml. of O_2 per liter, and that the arterial blood leaves the lung carrying 200 ml. per liter. Then each liter of blood has absorbed 55 ml. of O_2, so that the blood flowing per minute must be $\frac{220}{55}$ or 4 liters. It should be recognized that by such methods as this one can measure the output only when cardiac output and

oxygen consumption remain stable during the period of measurement (5 to 15 minutes). No adequate methods are at present available for the investigation of rapid changes. All the respiratory methods depend on this principle, which may be applied to O_2, CO_2 or to some foreign gas such as nitrous oxide, ethyl iodide or acetylene. In the case of a foreign gas, if the period of experimentation is short enough, the returning venous blood may be assumed to contain none of it and the problem is simplified. In the Grollman method a foreign gas is used but its rate of disappearance is not measured; by a differential method the *relative* rate of disappearance of the foreign gas to that of oxygen is used to estimate the oxygen content of venous blood.

Methods Utilizing Rate of Exchange of O_2 or CO_2.—The oxygen or carbon dioxide exchange may be readily measured, and the gas content of arterial blood determined by direct puncture of an artery and blood gas analysis, but it is obvious that an ordinary venous sample (e.g., from an arm vein) gives no indication of the *average* gas content of venous blood. For this reason various methods have been adopted to determine the composition of mixed venous blood.

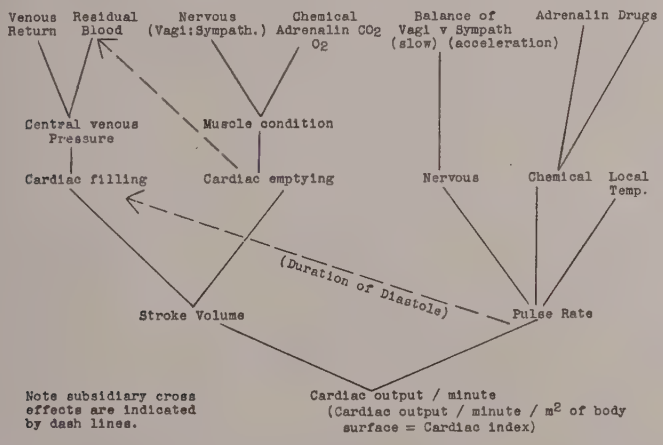


Fig. 146.—Diagrammatic representation of the factors which modify cardiac output per minute.

Estimation of Venous Gas Content by Heart Puncture.—Venous blood may be obtained by introduction of a needle into the right auricle or ventricle where mixing has occurred. The technique of heart puncture was introduced in 1919 by Barcroft, et al.[22] in work on goats. It has since been applied frequently to dogs, and occasionally even to man. The method may be illustrated by data obtained by Marshall[229, 230] on trained unanesthetized dogs. A dog weighing 15 kilograms consumed 76 ml. of O_2 per minute. Arterial blood contained 176.9 ml. and venous blood 132.6 ml. of O_2 per liter. The cardiac output was, therefore, $\frac{76}{44.3}$ or 1.72 liters per minute. Since the pulse rate was 85, the stroke volume was 20 ml. per beat per ventricle. After the vagal action had been paralyzed by an injection of atropine, the cardiac output remained unchanged (1.78 liters per minute), though the pulse rate was now 215. The stroke volume was, therefore, reduced to 8.3 ml.

Indirect Estimation of Venous Gas Content.—To avoid the danger of heart puncture many indirect methods of estimation have been devised. The oxygen and carbon dioxide tensions of venous blood have been estimated by finding the composition of a gas mixture which when introduced into the lung neither gives up nor acquires oxygen or carbon dioxide. The tension of the gas in such a mixture must equal that of venous blood, and from dissociation curves the gas content of the venous blood may be estimated. In practice such methods are difficult.[66]

Use of the Fick Principle With Foreign Gases.—When in following the Fick principle the experimental period is kept short the foreign gas content of the venous blood may be considered nil. The content in arterial blood may be estimated from the tension of the gas in the lungs and its solubility in the blood. In the nitrous oxide method devised by Krogh and Lindhard[206] in 1912 this was the case. The method is of historical interest, but also remains, with acetylene as a preferable gas, useful for measuring high cardiac outputs such as those accompanying exercise.

The Differential Acetylene Method of Grollman.[150]—At the present time this method or one of its minor modifications remains the most generally useful laboratory method for determinations on man. The apparatus is relatively cheap and portable, the technique simple in principle and fairly readily attained with practice. Oxygen consumption is found by any method available, e.g., a clinical apparatus for the determination of metabolism. A mixture of acetylene, oxygen and air is then rebreathed rapidly and forcibly from a bag. The volume of this mixture is *not measured,* but samples of the mixture are drawn into evacuated tubes after some 14 seconds of rebreathing and again at 18 seconds, while a later third sample may be drawn as a check. *The exact times are not important.* From analysis of these samples the average alveolar tension of acetylene is estimated, and from the solubility of acetylene the volume of acetylene removed per liter of blood is deduced.

The same analyses give the relative rates of disappearance of oxygen and acetylene, and from this comparison the volume of O_2 absorbed by the blood per liter is estimated. For instance, suppose that the acetylene removed by the blood is calculated to be 72 ml. per liter and that the acetylene was absorbed 1.3 times as fast as oxygen; then the oxygen absorption was $\frac{72}{1.3}$, or 55.4 ml. per liter of blood, and if, as before, oxygen consumption was 220 ml. per minute, the cardiac output must have been 220/55.4 or 3.97 liters.

The assumptions made are: that some 6 respirations in 14 seconds are required for adequate mixture in the lungs; that under basal conditions no appreciable recirculation of blood already in contact with acetylene occurs within 23 seconds; that, though the actual circulation rate is increased by the rebreathing procedure, the blood returned to the heart within the period used is blood that was already in veins and incapable of having its composition altered; that the mixing respiratory movements pump blood back to the heart from different areas in their normal proportions. Such assumptions are certainly not strictly true. Recirculation of blood probably is in evidence under basal conditions within 10 to 15 seconds (and when the circulation is more rapid even earlier than this), but the error introduced in the basal condition is small and is to a greater or less extent neutralized by errors of the opposite sign (such as reduced O_2 absorption with falling O_2 tension). For cardiac outputs that do not exceed a value of 2.5 to 2.8 liters per square meter of body surface per minute, the method is probably relatively accurate; for high outputs exceeding 3 liters per square meter per minute it is unreliable. It should be noted that the errors from recirculation tend to make the cardiac output appear low, so that the observer may have a false sense of security and fail to recognize when he is working beyond the method's accurate range.

Modifications of the method include the use of two bags and the introduction into the mixtures of CO_2 in a percentage equivalent to that of alveolar air (Gladstone[138]). It is claimed that in this way mixing may be attained more rapidly and the whole procedure completed in nine seconds, thus avoiding dangers of recirculation of blood which has already absorbed acetylene. Difficulties in mixing certainly occur in some individuals, and times intermediate between these and those of Grollman are likely ultimately to be adopted.

The Ethyl-Iodide Method as Modified by Starr and Gamble.[94, 288]—In this the Fick principle is followed. The subject is allowed to breathe quietly from a spirometer for some ten or more minutes a gas mixture containing ethyliodide (about 6 mg. per liter). From an analysis of the inspired and expired gasses the ethyl iodide absorbed is calculated; from the alveolar tension of ethyl iodide, and its solubility in blood, the arterial content is deduced. Venous content is low but not negligible, but since the gas is not involved in metabolism, a simple rebreathing procedure allows estimation of the venous tension and calculation of the content. This method needs no cooperation on the part of the subject and is, therefore, peculiarly suited for clinical work.

A difficulty of the method is the ready disappearance of ethyl iodide through rubber and grease, and the consequent necessity of using bags of light metal. Analysis is difficult, though it may be conducted rapidly and accurately by utilization of the gas' high thermal conductivity[94]; this technique involves elaborate and expensive apparatus.

Other Methods of Estimation.—The impossibility of applying the respiratory methods to seriously ill patients has led to attempts to find other methods.

Roentgen-ray photographs of the heart shadow taken with very short exposures at the start and end of systole and timed by the electrocardiograph have been utilized by Eyster and Meek[109] to determine cardiac output. This method has recently been developed by Keys.[202] It is difficult to obtain precision with it, particularly in the case of abnormal hearts, since the boundary between the auricles and ventricles cannot be distinguished and of course the auricles are filling at the time the ventricles are emptying.

Deductions of stroke volume have also been made by numerous workers from the pressure changes produced on expulsion of the blood into the aorta. As will be seen later, the time relations of the expulsion and the distensibility constants of the arterial tree are here important. The equations available depend on empirical assumptions.[33]

Another principle that has been utilized is the measurement of the recoil resulting from the expulsion of blood. When blood is ejected into the aorta, not only is the apex of the heart forced downwards against the diaphragm by this recoil, but also the whole body and even the bed on which the subject lies. These movements were investigated by Yandell Henderson,[163] and more recently by Starr.[289] The latter has built an instrument—the ballistocardiograph—to measure these thrusts. The records obtained are very complex, especially in cases with abnormal circulations, since thrusts from the recoil of the heart are fused with others caused by the diversion of the stream into new directions. Like electrocardiograms, ballistocardiograms may prove of considerable value, but only after empirical rules have been established by experience.

CARDIAC OUTPUT IN MAN

The Basal Value.—Under basal conditions the cardiac output in human beings is 2.0 to 2.4 liters per square meter of body surface per minute. The stroke volume is, therefore, some 30 to 40 ml. per square meter. It varies with the pulse rate. According to Starr and his associates[288] the minute output is more closely related to body weight than to surface area and averages about 64 ml. per kilogram per minute. It is higher in the adolescent than in the adult and decreases in subjects over forty-five years of age. The basal does not represent the minimal value in the normal subject. Sub-basal values are found in the early hours of the morning,[150] during standing and probably also during recovery from heavy exercise.

The normal basal cardiac output has an absolute value of 4 liters per minute for an individual of average size (1.8 square meters body surface) and, if the pulse rate is 70, the stroke volume is 57 ml. In 1733 Stephen Hales[151] estimated the cardiac output in man on the basis of the earlier estimates of Harvey and Lower and his own data on dogs. The calculations were based on ventricular volumes obtained from casts. His estimate for a dog weighing 20 kilograms was 4.34 pounds or about 2.0 liters per minute; for a normal man it was 9.36 pounds or almost exactly 4 liters per minute. He considered that the normal stroke volume in man is 54 ml. The agreement with modern figures both for the dog (compare Marshall's values, p. 399) and for man is remarkable.

The Effect of Posture.—The cardiac output is usually reduced when the subject stands. Oxygen consumption and pulse rate are normally increased, so that the oxygen utilization of the blood is greater and stroke volume is reduced. The latter appears to depend on poor venous return from the lower part of the body in prolonged standing *without movements.* According to Grollman[150] there is no reduction, but other workers[94] disagree with him. Under some conditions the reduction on standing is so slight that it falls within the experimental error. This is common after a prolonged period of hot weather.[281]

In the sitting posture the cardiac output may be below that found when the subject is reclining, but the average values do not show any considerable difference.

Cardiac Output in Sleep.—Though Grollman found low values in the early hours of the morning, he did not find any significant difference between the cardiac outputs of the sleeping and awakened subject.

The Effect of Ingestion of Food.—The cardiac output is increased considerably after a meal and to a less extent after the ingestion of large volumes of water. The increase in pulse rate and cardiac output is immediate. These initial changes are doubtless partly due to the muscular exercise incident to eating. After the initial change there may be a fall toward a basal value. This is followed, some thirty to forty-five minutes after the meal, by a second increase which is probably contemporaneous with digestion and absorption. The augmented output may continue with moderate fluctuations for several hours. In subjects not previously starved the initial increase in output is associated with a faster pulse and a stroke volume which remains unchanged or increases.[150] In subjects exposed to long-continued deprivation of food and fluid (seventeen hours or more) the increase in pulse rate is marked and the stroke volume is usually reduced.[37] In such conditions the rapid outpouring of digestive juices may lead to a temporary decrease in venous filling.

The Effect of Anoxemia and CO_2 Excess.—The anoxemia produced by a high altitude causes a gradual increase in the cardiac output. This reaches a maximum after about five days' exposure to the low oxygen tension, whereupon it gradually returns to a normal value. Excess of carbon dioxide slows the heart rate in dogs, and increases the stroke volume, leaving the minute volume little altered, but if the percentage of CO_2 in inspired air exceeds 5 per cent, the minute volume may be reduced somewhat. In man increase in the percentage of CO_2 breathed has no effect until it rises above 6 per cent; then it produces an increased output. Some of these effects appear to be secondary to the effects of increased respiratory movements on venous filling. Grollman[150] found that voluntary hyperpnea increases the output, probably for the same reason. Contrary results were obtained by Christiansen, Douglas and Haldane[66] with a different method. Probably either change may occur. The direction will depend on the degree of hyperventilation and the individual type of reaction.

The Effect of Temperature Changes.—Exposure to cold slows the pulse and increases the stroke volume. It leaves the minute volume unaltered, unless the change is excessive and produces marked shivering. Then the output is increased and the pulse rate raised somewhat. Exposure to warmth increases the cardiac output very considerably. The pulse rate is increased with a slight reduction in stroke volume, but if exposure to heat is continued and leads to dehydration, there may be a return of the cardiac output to the basal level in spite of a high oxygen consumption and fast pulse rate. Venous return is then inadequate. Pyrexia induced by typhoid vaccine also causes an increased cardiac output. Pulse rate and stroke volume increase initially, but with prostration there is a reduction in the stroke volume. The increase in cardiac output is at first commensurate with the increased metabolism, but it subsides earlier.

Cardiac Output During Muscular Exercise.—Data have been obtained during exercise by both the Krogh and Lindhard and the Grollman methods.[65] Though consistent values may be obtained, systematic errors are not unlikely and it is difficult to believe that recirculation of blood already in contact with

the foreign gas has not occurred. The cardiac output can certainly be enormously increased during exercise. The high cardiac outputs that must accompany the high oxygen consumption of exercise have been emphasized by A. V. Hill.[172] The principles involved may be illustrated by recent data obtained on well-known athletes and reported by Robinson, Edwards and Dill.[264] Some of these data were obtained on Lash at the end of a two-mile run for a world's record. They found that this subject breathing ordinary air was able to attain during severe exercise an oxygen intake of 5.35 liters per minute. At the end of such an effort he had a pulse rate of 190 per minute, and blood with an oxygen capacity of 245 ml. per liter. While it is possible that blood may leave the active muscles almost completely unsaturated, blood from the brain and skin must have contained a considerable amount of O_2. The saturation of mixed venous blood in the right auricle can scarcely have been below 20 per cent, certainly not below 10 per cent. The oxygen taken up by each liter of blood consequently, may have averaged 195 and cannot have exceeded 221 ml. The cardiac output per minute may be assumed, therefore, to have been between the limits of $\frac{5.35}{0.221}$ and $\frac{5.35}{0.195}$ or between 24. 2 and 27.5 liters per minute. At the former value the stroke volume would be 127 ml. and at the latter 144 ml.

During exercise there is therefore not only a great increase in pulse rate, but a great increase in stroke volume. The venous return must be extremely rapid and adequate to distend the ventricles to a considerable pressure. The results are in strong contrast with those obtained when the pulse rate is increased by paralysis of the vagus by atropine (see page 399). In this case venous return is little altered, and the increase in pulse rate causes little increase in the cardiac output per minute.

Cardiac Output in the Damaged Heart.—Compensation (see page 396) may be attained, so that the cardiac output at rest is normal. In such *compensated cardiac patients* the difficulties arise from the utilization of their reserve cardiac power and a consequent inability to meet additional strains. The value of the cardiac reserve may be demonstrated by tolerance or intolerance to exercise. Persons with valvular lesions, particularly aortic regurgitation, may be able to undertake heavy work, if their cardiac muscle is undamaged. They are rarely able to compete in endurance tests and they should not attempt it, since the extra work demanded from the heart may be very great.

When the compensatory mechanisms are exhausted and yet the cardiac output is inadequate either for conditions of rest or minimal activity, the heart condition is said to be *decompensated.* Such a heart is already utilizing all its reserves. Acute cardiac failure with a rapid reduction of cardiac output may develop. This results in venous engorgement and raised venous pressure, and since no further compensation is possible, cardiac dilatation may exceed the optimal value and become a liability.

Chronic cardiac failure shows a similar picture but one complicated by marked venous engorgement, usually associated with both raised venous pressure and increased blood volume. Such a chronic state is known as *congestive heart failure.* Considerable discussion has arisen as to the pathological changes involved. Cardiac output is not readily measured by the respiratory method in the presence of severe symptoms. Such data as are available indicate that cardiac output may be considerably reduced (to a level only 55 to 60 per cent of the normal basal value) or may almost attain the normal level. There appears to be little correlation of the level of cardiac output with the severity of the

symptoms. This has resulted in emphasis being placed on the venous changes. In reality the reduction in flow and these resulting compensatory venous changes are merely two aspects of the same process.

The cardiac output must be evaluated in accordance with the demands of the tissues for oxygen. Some subjects may live at such a low sub-basal level of activity (the basal cardiac output is not the minimal level at which a circulation may function normally) that a subnormal cardiac output is not serious. Some subjects, on the other hand, may have valvular damage, so that the work the heart has to perform is much increased; the oxygen needed by that heart and consequently the coronary blood supply may also be much above normal. Or again the muscle tissue of the heart may be so damaged that the mechanical efficiency is very subnormal; here too an increased coronary supply is a necessity. Any combination of these conditions may be present. When a high coronary flow has to be maintained, a normal level of cardiac output for the left ventricle does not necessarily imply a normal peripheral circulation, even at rest. With the mildest activity (e.g., meals) the peripheral flow may readily become markedly subnormal. A reduction of peripheral flow maintained constantly may be serious, even if it amounts only to a reduction of 10 to 20 per cent. The lowered flow automatically increases venous pressure, but in the chronic, as contrasted with the acute, failure new factors are introduced. Probably other compensatory mechanisms which tend to raise venous pressure and cause cardiac dilatation are evoked. Among these is an increase in blood volume. The venous congestion and raised venous pressure that result may be excessive, and cause abnormalities of fluid balance (edema), as well as cardiac dilatation, beyond the optimal value.

Circulation Time

The need of measuring the velocity of blood flow in man, particularly in ill patients, has led to the measurement of the rate of transference of substances from one area to another by the blood. Sometimes the test substances are injected into the external jugular vein in the neck, and the pulmonary circuit is then mainly responsible for the time consumed. More commonly they are injected intravenously at the elbow, and the time includes that taken in transit in the large veins. Various substances have been used, and the criteria of their occurrence in the arterial circulation have consequently varied. Among the substances employed are decholin, saccharine (giving a bitter or sweet taste), histamine (skin flush), and radium emanation (electroscope test). One which has had considerable use is a 2 per cent solution of sodium cyanide injected intravenously in a dosage of 0.066 to 0.11 mg. per kilogram (the smaller dose if the jugular be employed). This drug depresses oxidation and stimulates the carotid and aortic bodies as does oxygen lack (see page 584); there results a marked but very temporary hyperpnea when the drug reaches these points. In cases with cardiac decompensation the average time from the arm injection to the generation of such symptoms is 23.2 seconds, as compared with a normal of 15.6 seconds (from the jugular the normal time averages 10.6 seconds). But the results are variable; normal times may be as long as 21 seconds.[258] Though differences are statistically significant, figures from an individual case need not indicate conclusively a slowed circulation.

The measurements so obtained demonstrate only gross changes. Much of the time consumed depends on the flow along a vein into the chest. This flow represents the conditions only in a local area and may vary considerably with such things as the temperature of the environment. There is no close correlation with the results of measurements of the whole cardiac output. This is not surprising. Measurement of cardiac output determines the whole cardiac output including that through the coronary arteries. If the heart is damaged and working inefficiently the coronary flow may represent an abnormally large proportion of the total flow. Cardiac output measurements may therefore also be deceptive in regard to the blood supply to the body as a whole. Only by critical evaluation of all available data can estimates be formed of the state of the circulation under pathological conditions.

CHAPTER XXXII

THE PERIPHERAL SYSTEMIC CIRCULATION

The systemic circulation forms the larger of the two sections of the closed circulatory system. It consists, as has already been stated, of distributing arteries, a capillary system for exchanges of substances between blood and tissue fluid, and collecting veins. These various parts must now be considered in more detail, for they all exert their own functions in the circulation. The smaller arteries, or arterioles, have strong muscular walls, and can offer considerable resistance to blood flow. They can thus control the distribution of blood to different areas. The resistance to flow offered by these vessels, coupled with the high distensibility of the more central larger arteries, also has an important effect in converting the intermittent flow of blood from the heart into the aorta into a continuous flow in the capillaries. The high resistance of the arterioles prevents the immediate discharge of blood into the capillaries at systole, and the highly distensible arterial reservoir is able to accommodate during cardiac systole much of the blood ejected, without any great rise in pressure. It can then discharge it during cardiac diastole. The elastic system therefore not only minimizes fluctuations in the peripheral rate of flow, but also fluctuations in pressure in the central vessels. The capillaries play an important role in regulating the nutrition of the tissues and in maintaining fluid balance. The veins not only collect the blood but also function in the dissipation of heat in the periphery and act as large reservoirs of blood.

THE ELASTIC RESERVOIR OF THE CENTRAL ARTERIES

The elastic properties of the arteries are complex. Their walls consist partly of highly distensible elastic tissue, partly of muscle, the contractile condition of which may be varied, and partly of a loose coat of relatively indistensible white connective tissue. Conditions in the vessels are necessarily determined by the mathematical relationships of tubes. The volume contained in a section of any given length must vary as the square of the radius; pressure within a tube is more effective in producing a stretch of the wall the larger the radius of the tube. The increase in radius for any given increase in pressure is therefore a function of the original radius. As a consequence of these relationships the increase in volume accommodated through an increase in pressure (if there is no change in the constants of elasticity) varies as the cube of the radius. It is obvious that a small change in the diameters of vessels will produce a considerable change in their capacity to accommodate blood.

As soon as growth ceases and adult age is reached, the blood vessels commence to undergo age changes which lead to a loss of distensibility. These may be compared with the changes which rubber tubing undergoes as it "perishes" and hardens with age. During the process of aging, rubber tubing tends to assume any larger size, to which it has been stretched. So too the larger blood vessels not only harden and become less distensible, but also assume under resting conditions larger diameters. They fail to regain com-

pletely their original size after they have been stretched by increases in pressure. The loss of distensibility of advancing age is to some extent compensated by this increase in size of the vessels, for any given stroke volume implies a smaller *percentage* change in volume. The changes in the size of the aorta which occur during life (as found at autopsy) are shown in Fig. 147. The effect of age is obviously great. Up to middle age loss of distensibility is compensated (except at the high pressures that accompany heavy work) by a steady increase in the cross-sectional area of the aorta. In the later decades the effects of loss of distensibility usually outweigh those due to increase in vessel size even at the lower pressures of resting conditions.

The change in distensibility that develops with age is shown in Fig. 148. The per cent increases in volume of aortas of subjects twenty-two, thirty-nine, and seventy-five years of age, respectively, are here shown as functions of the internal pressures. It is clear that the curve for the young aorta is S-shaped; it shows an initial increasing distensibility as the internal pressure is increased. This increasing distensibility depends on

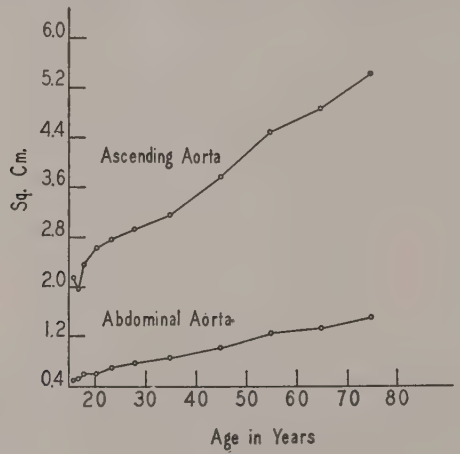


Fig. 147.—Relation of the cross-sectional area of the aorta in man (ordinates) to age (abscissae). Drawn on basis of data reported by Thoma and analyzed by Hess.[109]

the characteristics of elastic tubes. The decreasing distensibility of such aortas at the highest pressures and larger volumes depends on the effect of white fibrous tissue. With pressures less than 90 mm. Hg the distensibility of the aorta of subjects thirty-nine years old is actually greater than that of the younger subject. This too is due to the characteristics of tubes. It depends on the enlargement of the aorta with age (see Fig. 147) and the consequent more effective development of transverse stretch in the wall as the result of pressure changes within the vessel. The data indicated in Fig. 148 show that at higher pressures the loss of distensibility is dominant, particularly in the aortas of the older subjects. By utilizing the data shown in Fig. 147, or the original data published by Hallock and Benson from which Fig. 148 is derived, estimates may be made of the absolute cross sectional areas of the aorta at various ages when distended at different pressures. The deduction may be made that at a pressure of 180 mm. the cross-sectional areas of aortas of subjects of thirty-nine and seventy-five years of age are almost identical. The undistended aortas of subjects aged thirty-nine are much the smaller. Consequently, the aortas of subjects aged thirty-nine increase at a pressure of 180 mm. to a cross sectional area 2.58 times the undistended value, while in subjects aged seventy-five, the increase is only to one 1.84 times that value. With younger subjects, aged twenty-two, the distensibility is greater throughout the range. Not only is the cross-sectional area of the undistended aorta smaller than that

found in either of the other age groups, but also the area for the aorta distended at 180 mm. is larger. The change with an increase in pressure to 180 mm. is in these subjects to an area 3.45 times the undistended value.

The efficiency of an aorta to store blood ejected by the heart is determined by the cross-sectional area of the aorta at the diastolic pressure and by the distensibility of the aorta at pressures in the range between diastolic and systolic pressures. This efficiency may be gauged by the pressure increase imposed by the storage of any given volume of blood. In the construction of the curves of Fig. 149 estimates have been made of the probable increases in pressure for an assumed storage of 30 ml. The normal stroke volume of an adult man is about 60 ml., so that the assumption implies that half of this stroke volume is stored during systole to be discharged into the smaller vessels during diastole. To estimate the pressure changes it has been assumed that the aortas have volumes determined by the cross-sectional areas indicated by Hallock and Benson's data and are 50 cm. in length. These volumes are merely nominal and not real volumes, though the ratios between them should be roughly the same as those between the real volumes. Values have been calculated for various diastolic pressures in five of the age groups described by Hallock and Benson.

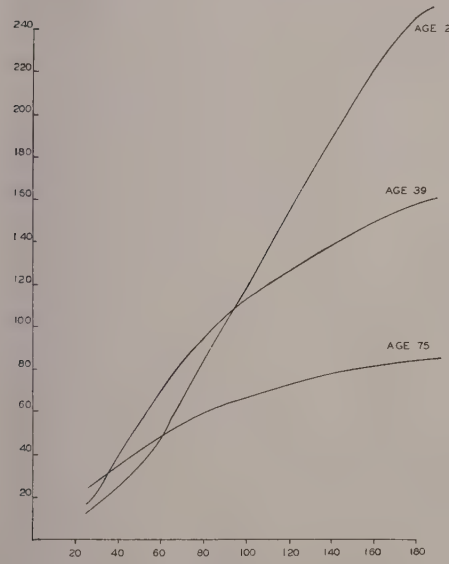


Fig. 148.

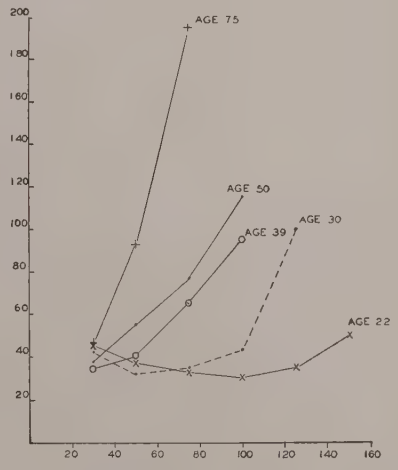


Fig. 149.

Fig. 148.—Curves describing the distensibility of the thoracic aorta at different ages. The per cent increases in volume above the undistended levels are plotted (as ordinates) against the distending pressures in mm. Hg (as abscissae) for thoracic aortas of different age groups. (Redrawn after Hallock and Benson: J. Clin. Investigation **16**: 595, 1937.)

Fig. 149.—Curves showing the relationship between diastolic pressures (abscissae) and the increases in pressure or pulse pressures (ordinates), which theoretically would be produced by the systolic storage of 30 ml. of blood. The values are calculated from the distensibility curves given by Hallock and Benson (J. Clin. Investigation **16**: 595, 1937), and nominal diastolic volumes for the aorta are estimated on the basis described in the text.

The data used in constructing Fig. 149 indicate that in the youngest group (age twenty-two) storage is attained with less pressure disturbance the higher the diastolic pressure, provided it does not exceed a level of about 100 mm. Hg. This beneficial effect depends on the properties of elastic tubes and is determined by the greater cross-sectional area of the aortas at the higher diastolic pressures. By the age of thirty this effect is lost through decreased distensibility, though there is little real inefficiency except at quite high diastolic pressures. At ages thirty-nine and fifty storage of blood is much less efficient except at quite

low diastolic pressures. At the age of seventy-five efficient storage cannot be obtained except at impossibly low diastolic pressures. At this age systolic flow has to be greater and even so pulse pressures are necessarily much exaggerated.

PERIPHERAL RESISTANCE TO BLOOD FLOW

Blood Viscosity.—The effective peripheral resistance may be defined as the frictional resistance offered to flow by the arteries, arterioles, capillaries, and veins, especially the arterioles. This depends on the viscosity of the blood. In the case of any fluid which wets the walls a layer of fluid adheres to the wall and the frictional resistance depends on the shear in the fluid between this layer and the moving central stream. The viscosity of colloid solutions is complex, that of such a solution containing also a suspension of larger particles (red blood cells) even more so. The viscosity of blood plasma is about 1.5 to 1.7 times that of water; it varies with the protein concentration. The viscosity of whole blood varies with the corpuscular content. The apparent viscosity of any given suspension also varies with the conditions of its measurement; the apparent viscosity is less the greater the velocity in the tubes (up to a certain critical velocity), so that in Hess' method of measurement[166] a considerable pressure is used to give a relatively high velocity, and the value obtained is constant and lower than that obtained with smaller driving pressures. The mean value obtained for human blood by Hess' method is, in comparison with water, 4.7 (4.3 to 5.3) for normal males and 4.4 (3.9 to 4.9) for normal females. Such values probably apply to the flow of blood in the larger vessels but in the smaller arteries and arterioles in which the main resistance is developed, the actual effective viscosity is probably much less. This was demonstrated by Fåhraeus and Lindquist,[113] who found that the apparent viscosity of a blood suspension varies with the size of the tube used in the test and is not so great relative to water in tubes of less than 0.3 mm. diameter. Careful study of the fluid left in such a tube gave the clue to the cause; the fluid leaving has the same composition as the entering fluid, but that contained in the tube has fewer corpuscles. As the initial blood enters the tube, part of the plasma adheres to the wall, forming a plasma layer, and through this tube of plasma the blood moves. In a small tube this plasma layer is not a negligible value, so that during its actual passage through the tube the corpuscular suspension has a relatively low concentration and the viscosity is consequently reduced. Only the initial fluid that passes through the tube is altered in composition. When the blood enters the capillaries, the conditions are again altered. Here the vessels are often so narrow that the corpuscles cannot pass without being distorted, and the viscosity is then partly determined by the resistance of the corpuscles themselves to distortion. In an analysis of the viscous resistance to the passage of blood along the capillaries Landis[209] was able to substantiate this theoretical increase in resistance. The effective viscous resistance in the circulation as a whole has been determined by Whittaker and Winton[310] who measured the flow through a dog's leg perfused at different pressures by a pulsatile stream. With normal corpuscular contents blood has an effective viscosity of only about 2.2 times that of water. The effective viscosity varies with the corpuscular content, and the values obtained are shown in Fig. 150.

The viscosity of blood is commonly determined by comparing the rate of flow of blood with that of water or saline in similar tubes and at the same pressure. The viscosity of blood so determined varies with the conditions that obtain at the

moment. It is not an absolute value. The effective viscosity of physiological interest may be considered as that existing in the vessels under the conditions of normal blood flow. Even this is not a constant, for it varies not only with the composition of the blood, but also with the pressures existing in the arteries. Flows obtained in the perfusion of the leg of a dog with saline and with blood of normal composition are indicated in Fig. 151. The relationship of the two lines to each other at any pressure gives the effective viscosity of blood for that pressure. Thus at 60 mm. Hg the viscosity is $\frac{230}{80}$ or 2.88 relative to water, at 120 mm. $\frac{460}{210}$ or 2.19. At pressures below 20 mm. Hg all flow ceases when blood is used. According to these data the effective viscosity of blood in the vessels at pressures below 20 mm. Hg is infinite.

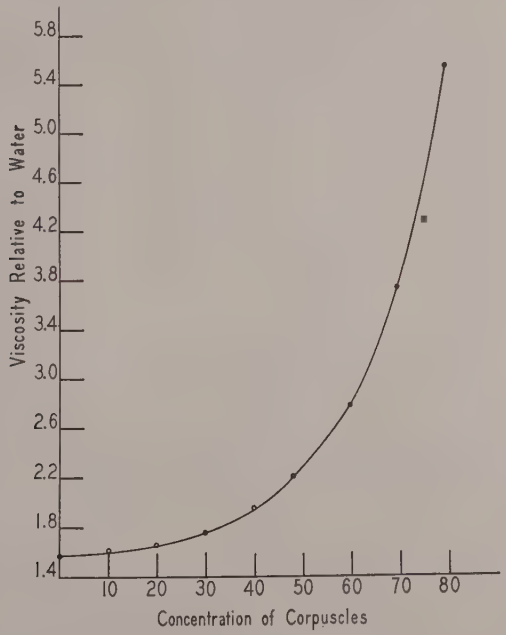


Fig. 150.—The effective viscosity of blood relative to water (ordinates) compared with the concentration (percentage volume) of corpuscles in the blood (abscissae). The values were determined by perfusion of the isolated leg of a dog. They represent the effective viscosity at a normal head of pressure. (Data of Whittaker and Winton: J. Physiol. 78: 339, 1933.)

The viscosities have been stated relative to water at 38° C. For more exact physical measurements they should be given in dyne-seconds per sq. cm. or poises; in these units the value for distilled water at 38° C. is 0.0068. It must be remembered that the viscosity of blood like that of water varies greatly with the temperature, and that the temperature of the blood in the peripheral areas is not uniform. A fall of temperature to 30° C. must cause an increase in viscosity of at least 17 per cent and a rise to 40° C. a decrease of at least 4 per cent. These temperature ranges are commonly exceeded in ordinary life, and the effect of local temperature increases resulting from muscular work on blood viscosity, and consequently on blood flow, must not only be significant but advantageous.

The Size of the Exit Vessels.—We have seen how blood viscosity plays a part in determining the resistance to flow. The size of the exit vessels and their number are even more important factors. As a tube is increased in size the cross-sectional area increases more rapidly than the surface where friction losses develop. Consequently at any constant pressure head the *velocity* of flow in a tube (if there is streamline motion) varies as the square of its radius and the volume flowing per minute varies as its fourth power. Small changes in vessel diameter in the arterioles can consequently have enormous effects on blood flow under a constant pressure head. It may be calculated that a reduction of 16.5 per cent in the circumference (or diameter) of a vessel would halve the flow through it, if the pressure head remained unchanged; it would double the pressure if the flow remained the same. One should bear in mind that changes of this sort may be present and yet remain unrecognizable at autopsy in patients

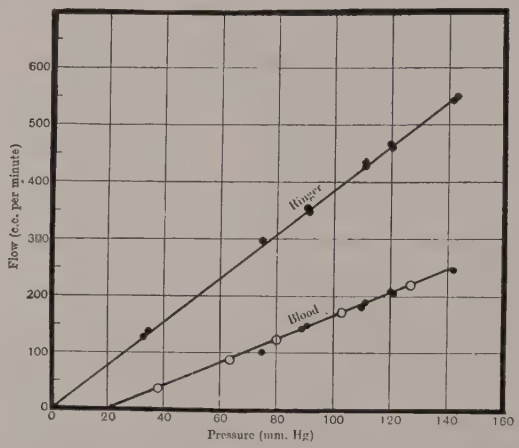


Fig. 151.—The flow per minute in milliliters (ordinates) relative to the mean arterial pressure (abscissae) in perfusion of the isolated leg of a dog. The open circles represent data obtained before perfusing with Ringer's solution, the closed circles data obtained after such perfusion. (From Whittaker and Winton: J. Physiol. 78: 339, 1933.)

who have suffered from increased peripheral resistance. A slight change, if widespread, would produce marked effects, and yet might be very difficult to recognize in pathological material by histological methods.

Owing to the effect of the size of the vessels the resistance to flow is greatest in the long and narrow arterioles where the flow is rapid; it is still considerable in the narrow capillaries in spite of the shortness of these vessels and the slow flow within them; it is least in the veins, with diameters which are much greater and rates of blood flow which are much less than those of the arteries. The effect of these resistances on the loss of pressure head has already been described.

Effective Peripheral Resistance and Arterial Pressure

The intermittent ejection of blood by the heart creates pressure fluctuations in the aorta, but owing to (*a*) the elastic reservoir maintained by the arteries and (*b*) the peripheral resistance, the pressure during diastole remains

much above the static level. The first pressures to be considered are the *systolic,* which is the maximal pressure developed during ejection, and the *diastolic* or minimal pressure, which occurs at the end of diastole. The difference between them is known as the *pulse pressure.* These fluctuations make the pressure vary on both sides of the average or *mean arterial pressure* which normally is at a level equal to the diastolic pressure plus ⅓ to ½ of the pulse pressure. The level of the mean pressure (which may be designated P_m) is determined by the resistance offered to outflow, on the one side, and by the inflow from the heart on the other. Thus if cardiac output be maintained constant and the resistance to outflow be doubled, the mean pressure must be doubled, for the resistance is measured in terms of the free energy required to overcome it. Or if the resistance be maintained constant and the cardiac output be doubled a greater pressure head is required to increase the rate of outflow and again the mean pressure is doubled. The relationship of cardiac output and peripheral resistance to mean arterial pressure is shown diagrammatically in Fig. 152. This may be correlated with the preceding diagram of Fig. 146 to which it may be fitted.

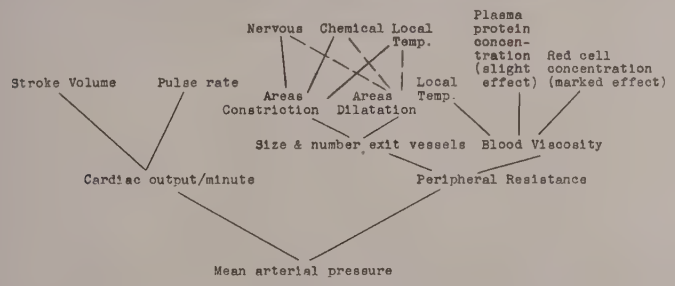


Fig. 152.—Diagram indicating the relationship of cardiac output and peripheral resistance to mean arterial pressure. The cardiac output per minute is greater and the peripheral resistance is smaller the larger the individual (larger heart and larger number of exit vessels). The values can be reduced approximately to comparable terms by dividing the cardiac output by the surface area of the body, which gives the cardiac index, and by using this value rather than the cardiac output to estimate the effective peripheral resistance.

While it is impossible at present to analyze separately the factors concerned in the total resistance with any quantitative exactitude, it is possible to estimate quantitatively their summated effect. It may be measured by the loss of free energy that it induces. Under most conditions practicable for study, this free energy is mainly pressure energy, so that it is justifiable to measure resistance by the loss of pressure energy. If R be the peripheral resistance, V_t the volume flow in unit time (usually taken as a minute), P_m the mean pressure in the arterial system, and K a constant, then this relationship may be written

$$R = K \frac{P_m}{V_t}$$

which is merely the reverse of the more frequently used expression

$$V_t = K \frac{P_m}{R}$$

In words, the volume flowing per minute is proportional to the pressure and inversely proportional to the resistance offered, or the resistance may be

measured by the pressure fall per unit of volume flow per minute. This provides a method of estimating the changes in peripheral resistance, for often both the mean pressure and the volume flow are known approximately.

Any such estimate of the resistance offered to flow has little meaning unless allowance is made for the size of the individual. Obviously a larger individual may have arterioles acting as exits which have the same diameters as those of a smaller individual but he may have many more of them. The absolute value of the resistance is then lower and the rate of blood flow higher. No method of exact quantitative comparison is known, but arbitrary comparisons may be made. Usually the volume flow is expressed as volume flow per minute per square meter of body surface (cardiac index); estimates of resistance may be related to flow thus measured.

Such arbitrary comparisons may be justified on the basis of the minor variations in blood pressure that accompany variations in size and the known dependence of cardiac output on either surface area or weight. Bazett et al.[33] found that if the mean pressure (in mm. Hg) be divided by the cardiac index, and the resultant figure be multiplied by 3, values for R may be obtained which in young subjects average about 100 and for the most part fall between 80 and 120. Such values may be used as rough standards of the *effective* peripheral resistance, when variations in the size of the individual play a minor role.

Schema of the Circulation

The physiological adjustments in the circulation are so complex and difficult to analyze that a schematic system in which single factors may be changed independently has many advantages. Numerous types have been described. Most of these consist of a pump and valves, but difficulties arise in that valves frequently leak, the magnitude of the stroke volume is not easily measured, and a pump which *lowers* venous pressure and which varies its action according to the venous pressure level is hard to devise. A type of schema which is simple to use, and valuable for analysis is one which attempts to reproduce only the arterial side of the system.* A large water reservoir is connected to a tap by tubing of wide bore. The level of this reservoir may be adjusted; it determines the static level of the systolic pressure. The simplest tap is a spring pinch-cock on rubber tubing opened by a motor-driven cam. The cam may be cut to give the normal ratio of systole to diastole for the pulse frequency used, and by a series of cams the pulse rate may be doubled or trebled, and the ratio of systole to diastole varied correspondingly. Beyond the tap the water runs into a simple elastic tube of thin rubber with one or more outlets. This represents the aorta. The outlets are connected by rubber tubing with broader glass tubes packed with heavy pipe cleaner wicks. The number of these functioning may be varied by clips on the rubber tubing and the effective peripheral resistance thereby altered. The pressure changes may be recorded with fair accuracy by manometers of the Hürthle type connected with either the central or peripheral end of the tube, or both. If the tubing has suitable length, diameter, and thickness, curves very similar to normal pulse curves are obtained. The dynamic systolic pressure rises 10 or 20 mm. above the static level at the peripheral end of the system, and very little above it at the central end. This is due to a wave effect. An increase in the peripheral resistance causes an increase in mean and diastolic pressure and a reduction in output. By raising the reservoir until the rate of outflow has returned to its previous level, the effect of varying peripheral resistance at constant output may be observed. Collection of the fluid at its exit allows an exact estimate of stroke volume. A central leak, controllable by a screw clip may be arranged to duplicate the effect of aortic regurgitation, provided that the cam is made to close this leak in systole at the same time that it opens the main tap. The development of much greater differences between static and dynamic systolic pressures at the peripheral end of the system is readily demonstrated. By changing the tubing, the effects of variations in distensibility can readily be shown.

*Such a schema is used for class work in the Physiological Laboratory at the University of Pennsylvania.

With such a schema it may be readily shown that the flow per minute is proportional to the mean pressure if the resistance is maintained constant, and is inversely proportional to the resistance if the mean pressure is kept constant. Thus the validity of the equation,

$$V_t = K \frac{P_m}{R},$$

may be demonstrated, as well as the other form of this equation, namely, that the mean pressure is determined by the product of the minute volume and the resistance. It may also be shown that if the distensibility of the system is unchanged, and if the pulse frequency (and consequently the pulse form) remains the same, the pulse pressure varies approximately as the stroke volume. The latter may be predicted from the size of the pulsations.

For any given stroke volume, the pulse pressure increases as the distensibility of the system decreases. Accordingly the stroke volume cannot be predicted from the pulse pressure when the distensibility varies.

Provided the distensibility remains constant, changes in stroke volume may be predicted accurately from the pulse pressure even when the pulse rate, and, consequently, the pulse form, are altered, if the systolic and diastolic phases of the pulse cycle are analyzed separately. The absolute fall of pressure in diastole is a measure of the decrease in contents during this period. In systole fluid is flowing both in and out. The outflow in systole is, however, related to that in diastole according to their relative durations and relative mean pressures. The systolic outflow can, therefore, be calculated from the diastolic, and the sum of the two is the stroke volume.

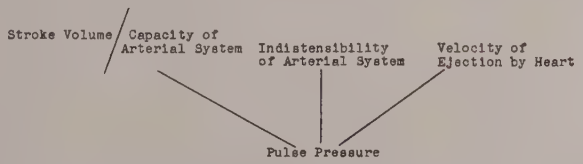


Fig. 153.—A diagram indicating the main factors which influence pulse pressure.

Diastolic and systolic pressure levels are seen to be determined by the mean pressure level and the size of the pulse pressure, which in turn is determined by the stroke volume and the distensibility. Though diastolic pressure commonly varies as the peripheral resistance, it does not necessarily do so, and is no indication of peripheral resistance. For instance, diastolic pressure is a definite function of pulse rate; if the cam be changed and the pulse rate be increased without any other change, owing to the alteration in the systole/diastole ratio, there will be a slight increase in output per minute. This increase may be obliterated by slightly lowering the reservoir. The mean pressure, resistance and output per minute remain unchanged after this adjustment, but the stroke volume is much reduced, and the pulsations on each side of the mean are smaller; diastolic pressure is raised, systolic pressure reduced. This is a change such as may be produced in an animal by giving a large dose of atropine, in which case the diastolic pressure is considerably raised, although there is no reason to assume any change in peripheral resistance.

The general effects obtained are shown in Table XIV. In this a rise in mean pressure is assumed to be associated with negligible effects on distensibility. It is true that in man or animals a rise in mean pressure is likely to be associated with a slight decrease in distensibility. The changes in stroke volume are shown under two possible conditions: one in which the stroke volume is altered while the pulse rate remains constant, and where, therefore, the cardiac output is proportionately changed; and another in which the pulse rate is inversely altered so that the cardiac output per minute is unchanged. Both types of change are common occurrences in the circulation. The corresponding primary changes in pulse rate are similarly listed.

It may be readily seen that changes in the pressure levels recorded from within the tube depend on the amount of fluid stored within it. When the pressure level is altered by altering the resistance or the pressure at which fluid is fed into the system. the new

level is attained by the storage, positive or negative, within the system of the required amount of fluid and dynamic equilibrium is not attained until this adjustment is completed.

The reader should be cautioned that such a system merely demonstrates the effect of a widespread change in the effective peripheral resistance. The effect of arteriolar constriction or dilatation locally on the flow through a single vessel may have no measurable effect on general arterial pressure. The contrast between the effects of local and generalized changes is discussed later.

TABLE XIV

FACTORS AFFECTING PRESSURES IN THE SCHEMA WHEN ADJUSTED (E.G., BY ALTERATION OF THE PRESSURES) TO MAINTAIN STARRED FACTORS UNCHANGED

FACTOR CHANGED	FACTORS SECONDARILY ALTERED OR ASSUMED UNCHANGED				PRESSURES			
	PERIPH. RESIST.	STROKE VOLUME	PULSE RATE	CARDIAC OUTPUT PER MIN.	MEAN	PULSE	SYSTOLIC	DIASTOLIC
Distensibility +	0*	0*	0*	0	0	–	–	+
Distensibility –	0*	0*	0*	0	0	+	+	–
Periph. Resist. +		0*	0*	0	+	0	+	+
Periph. Resist. –		0*	0*	0	–	0	–	–
Periph. Resist. +		–	0*	–	0*	–	–	+
Periph. Resist. –		+	0*	+	0*	+	+	–
Stroke Volume +	0*		0*	+	+	+	++	+
Stroke Volume –	0*		0*	–	–	–	– –	–
Stroke Volume +	0*		–	0*	0	+	+	–
Stroke Volume –	0*		+	0*	0	–	–	+
Pulse Rate +	0*	0*		+	+	0	+	+
Pulse Rate –	0*	0*		–	–	0	–	–
Pulse Rate +	0*	–		0*	0	–	–	+
Pulse Rate –	0*	+		0*	0	+	+	–

Note: Stroke volume × pulse rate = cardiac output per minute.

FACTORS AFFECTING ARTERIAL PRESSURE IN MAN

As has been stated already (see Fig. 152) the level of arterial pressure depends on a balance between cardiac output and peripheral resistance to flow. A normal level does not imply that either of these variables is necessarily normal; it merely indicates that the balance is normal. Similarly an abnormal level may be due to changes either in cardiac output or in peripheral resistance or in both. The factors involved have been presented in outline (Figs. 152 and 153) and in relation to a circulatory schema (page 412). As in the schema so in the arterial system an increase in cardiac output, whether produced by an increase in pulse rate or stroke-volume, will raise the mean pressure unless the peripheral resistance is simultaneously proportionately reduced. Also an increased stroke volume is commonly associated (in the absence of changes in the elastic constants of the vessels) with an increased pulse pressure. An increased pulse rate may be associated with an increased, an unchanged or a reduced stroke volume. If in the last case the changes balance one another so that cardiac output is not altered, mean arterial pressure tends to remain unchanged, while pulse pressure is reduced; systolic pressure tends to fall, diastolic to rise. An increased resistance raises mean, systolic, and diastolic pressure, but these changes are more complicated than is indicated in the schema. Vascular distensibility is usually affected by changes in the internal pressure.

The effects of changes in distensibility have been mentioned in relation to circulatory schemata. Decreased distensibility in itself increases the pulse pressure at any given stroke volume. If cardiac output and peripheral resistance

remain unchanged and the vessels become less distensible, mean pressure remains the same, and pulse pressure is increased; the systolic pressure is raised, diastolic lowered. In disease, changes in the resting size of the large vessels, in their distensibility and in the resistance offered to flow by the smaller vessels commonly occur simultaneously.

MEASUREMENTS OF ARTERIAL BLOOD PRESSURE

Methods of measurement are essential, if blood pressure and its regulation are to be investigated. The earliest attempt to accomplish this was made by the English scientist, the Rev. Stephen Hales,[151] in 1733, a little over a century after Harvey published his account of the circulation of the blood. Hales connected the severed artery of a horse to a vertical glass tube 9 feet long, and in making the connection utilized the windpipe of a goose. He found that the blood rose to a height of over 8 feet above the level of the left ventricle, and that the level fluctuated through 2 to 4 inches with each pulse beat. The mercury manometer was applied to the problem in 1828 by Poiseuille and was modified by Ludwig in 1847 to allow graphic records to be obtained from a float on the mercury, so that progressive changes could be studied. These advances, assisted by the invention of rubber tubing and the introduction of anesthesia, allowed a study of blood pressure changes in animals to be made under conditions more nearly normal than those previously attainable. The great inertia of mercury makes it suitable only for recording the mean, or average, pressure; it is incapable of following with any accuracy the rapid pulsatile changes in pressure which occur with the intermittent expulsion of blood by the heart.

To record the magnitude of the fluctuations, systems with less inertia such as the membrane manometer devised by Hürthle, were introduced. These were followed by manometers devoid of levers, in which all magnification was attained by a beam of light impinging on a mirror, as in the instruments designed by Otto Frank (see Wiggers[314]). Such instruments may give accurate measurements of the rapid pressure changes; the mean pressure level is, however, not directly indicated, though it may be derived by graphic integration of the curves.

In 1896 Riva Rocci described an indirect method of measuring arterial blood pressure in man. It involves simply the determination of the air pressure which, when applied to a cuff on an arm, is necessary to obstruct the blood flow. The development of this technique by von Recklinghausen, Erlanger and Hooker,[104] Korotkow and many others has considerably enlarged our knowledge. Under the leadership of von Recklinghausen[252] the tendency has been to attempt to develop recording systems of higher natural frequency, which will allow a study of the pulse forms as well as a more accurate estimate of the magnitude of the changes in pulsation during compression and decompression.

Direct Measurement of Arterial Pressure in Animals and Man

Methods of Measurement.—*The Mercury Manometer.*—This consists usually of a glass U-tube partly filled with mercury, though a simple vertical glass tube rising from a larger mercury reservoir may be used. In the former type one side of the U-tube is connected by tubing to a cannula inserted in the artery of the animal, and this is filled with some anticoagulant fluid, usually a saturated solution of sodium citrate. Side tubes on the connecting tubes allow the system to be washed free of blood which may pass into it during marked changes in pressure. A pressure bottle is connected to one of the side tubes of the system to generate within it, before it is connected with the artery, a pressure approximately equal to that in the animal, so that the amount of blood utilized in displacing the mercury may be negligible. This type of manometer may be connected with the animal by any convenient length of tubing, since the length of the connection has little effect on the type of record.

When an artery is connected with such a manometer, the pressure within it forces mercury into the distal part of the U-tube until the mean (average) arterial pressure is attained. Fluctuations occur on either side of this level but they are small, and vary more with the pulse rate (slow pulsations are more effective in a system with such inertia) than with the real magnitude of the fluctuations in arterial pressure. Magnification is good (50 mm. for 100 mm. of pressure) and, consequently, slow rhythmical variations, such as those due to respiration, are well indicated, and may appear as large as, or larger than, the inadequately reproduced, though really larger, pulsations due to the heartbeat.

Usually a light float is used to record the fluctuations in the level of mercury on the far side of the U-tube. The modern introduction of methods for puncturing the large arteries (brachial, femoral and radial) with needles has allowed direct estimates to be made in this way of the mean pressure in man, for such needles may be connected, under aseptic precautions, with a mercury manometer. Such measurements have given little new information, owing to the inherent limitations of the mercury manometers; even the mean pressure is not well indicated, as only a short time elapses before clotting occurs in the needles, and during this short period, as the result of the excitement associated with the puncture, the individual may not have a normal pressure.

The Membrane Manometer.—By the use of a rubber membrane manometer the inertia of the recording system may be greatly reduced. This type of instrument may utilize a simple heavy rubber membrane with a short light lever for magnification. In place of a rubber membrane combinations of rubber, of fluted metal, or thin glass plates with a spring may be used.

Fig. 154 represents Hürthle's type, which combines a spring resistance with that of a heavy rubber membrane. Such manometers must be connected with an artery by as short a length of tubing as possible, and preferably with tubing of considerable diameter

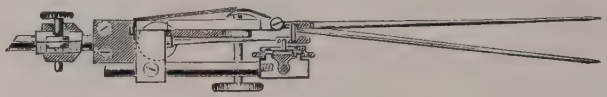


Fig. 154.—Hürthle's spring manometer.

(1 to 2 cm.), so as to reduce the velocity and momentum of the moving fluid; air bubbles must be absent and distensible rubber connections reduced to a minimum. The writing lever should be short and very light. The manometer must be standardized by connecting it with a pressure bottle or mercury manometer, and the displacement of the point for each 20 mm. Hg increment in pressure must be recorded. Such manometers (if the kinetic energy associated with fluid movement in the connecting tubing be kept within reasonable limits) may have a natural frequency of 10 to 40, or more, double vibrations per second, as compared with one of about 2 for the mercury manometer. Magnification is, however, small, and greater magnification can only be attained at a sacrifice of the natural frequency and, consequently, of the fidelity of the records. In the manometers usually used a lever excursion of 10 to 20 mm. represents 100 mm. of Hg. If a tap be used to constrict the tubing connecting the manometer with the artery, the pulsations may be almost damped out, and the instrument then records mean pressure; if the tap be partially opened, the size of the pulsations with each heartbeat, the level of the maximum pressure reached in the cycle (the systolic pressure) and of the lowest pressure (the diastolic pressure) may be more or less truthfully recorded. If the tap be fully opened, overfling from momentum may exaggerate the height and depth of systolic and diastolic pressures. According to the balancing of errors the pressure differences between these two levels (the pulse pressure), the height of the maximum, and the depth of the minimum pressure reached in the intervals between beats may all be either exaggerated or minimized. Owing to the small exchange of fluid with each beat, the system does not get contaminated unduly with blood. A simple straight cannula and tubing without branches may be used for connecting the instrument with the animal, provided that the whole system is free of air bubbles. For the same reason records may be obtained for hours without trouble from clotting; this is rarely the case with a mercury manometer.

Optical Manometers.—By utilizing a mirror and light beam instead of a lever to attain magnification, instrumental inertia may be enormously reduced, but such gains are nullified unless the connecting system is also relatively free from inertia. Consequently, these recording

instruments consist of a single unit of manometer and connecting glass tubing; the latter is attached directly (with no rubber connections) to the vessel by a broad cannula. The membrane is usually of heavy rubber, though a glass plate is employed by Broemser[50] and a thin metal membrane by Hamilton et al.[158]

Manometers of the last two types permit so little fluid movement that they may give true records of the fluctuations even if connected to an artery by narrow tubing, such as that of a hypodermic needle. For other optical manometers the cannula must be broad to ensure accuracy. Consequently direct estimations of the fluctuations in man can only be obtained with manometers of the Hamilton or Broemser type.

Fig. 155 represents Wiggers' type of optical manometer;[314] it may be noted that in spite of the ball and socket joints, the animal has to be adapted to the position of the manometer rather than the reverse. Greater adaptability is hard to attain by the ordinary type of

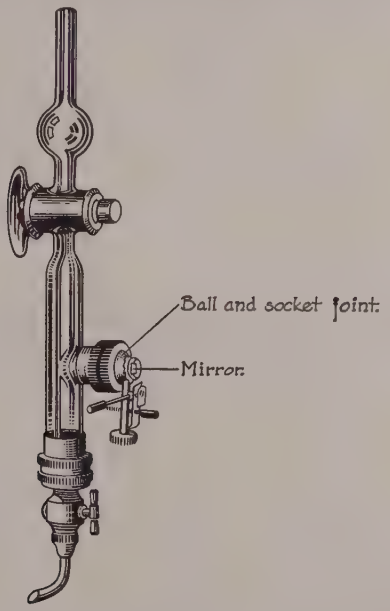


Fig. 155.—Wiggers' optical manometer. The pressure changes are recorded by reflection of light from a mirror attached, as indicated, to the small rubber-covered tambour of the "segment capsule." A second adjustable mirror records the base line.

optical manometer. The recent application of piezoelectric crystals to blood pressure measurements,[54] if developed on sounder physical principles, may solve the instrumental difficulties, for in this case electrical transmission to any convenient situation can be attained without distortion. Another type of electrical transmission manometer has been described by Wagner.[303]

The relative values of the various methods may be seen in Fig. 156 where records obtained from the femoral artery of a dog before and after stimulation of the vagus nerve in the neck are reproduced. The upper tracings are optical records obtained with a Wiggers' optical manometer on paper moving 15 mm. per second; below the pressure records the true base line has been indicated. The electrocardiogram (Lead II) is also shown. The manometer had a natural frequency of over 150 a second, and gave a deflection of 1 mm., for each 7.8 mm. Hg. The values recorded may be regarded as absolute, though with such magnification careful reading is required. In the pulses immediately preceding vagal stimulation in the two records the systolic pressures were 124 and 116, and diastolic 84 and 81; the mean

pressures (estimated by graphic integration of the curves) were, respectively, 95 and 92. Below in A is shown a record obtained at the same time with a membrane manometer connected to the other femoral artery. The manometer used was undamped, was connected (as commonly used for class work) by relatively long lengths of tubing, and the straw lever was relatively heavy. The natural frequency of the system was only 12 per second, the paper travelled more slowly (5 mm. per second) so that the whole period of vagal stimulation is shown. The curve obviously gives the same general picture as does the optical manometer, but systolic pressure is exaggerated by lever over-swing. The estimate of mean pressure is correct. Pulse pressure is exaggerated, and the magnitude of the error is found to vary with the suddenness of the initial pressure rise. Below in B is shown a record obtained with a mercury manometer (with a natural frequency of 3 per second) simultaneously with the optical record shown above it. Here the mean pressure may be read off directly with considerable accuracy and the value agrees with the other estimates. The curves are distorted and no indication is given of the magnitude, or even the direction, of the changes in pulse pressure.

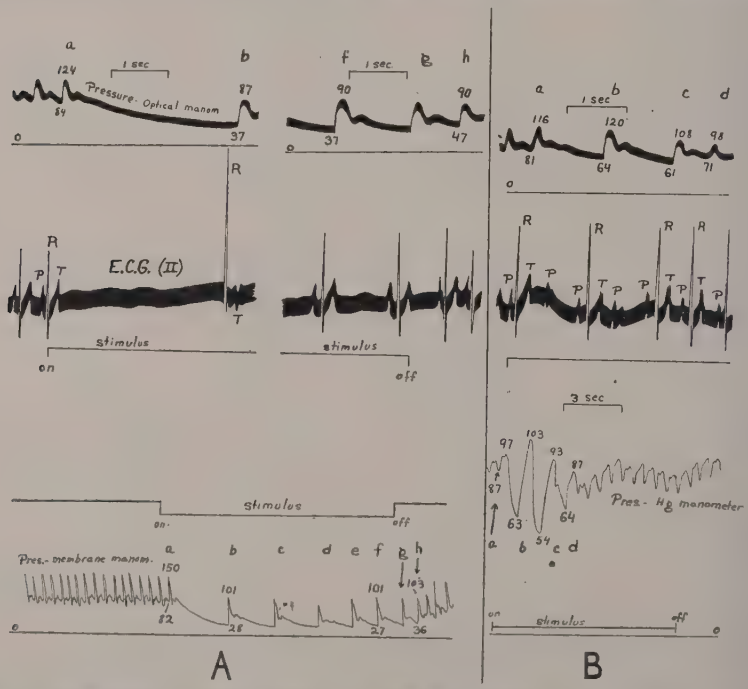


Fig. 156.—Records (redrawn) obtained by different manometers of changes in pressure in the carotid arteries of a dog. Changes produced by stimulation of the peripheral end of the cut vagus (right nerve in *A*, left in *B*). The uppermost records in both *A* and *B* were obtained by an optical manometer connected with one carotid artery. The pressure in the other carotid was simultaneously recorded (lowermost record) by a membrane manometer (in *A*) or a mercury manometer (in *B*). Electrocardiograms are shown below the optical records; some of the electrical waves are labelled. Only a few pulse cycles are reproduced in each record, but these are identified for comparison by *a*, *b*, *c*, *d*, etc. The apparent systolic and diastolic pressures of some of the cycles, as recorded by the different systems, are indicated by numbers; only those recorded optically can be considered correct.

Distinction Between End and Lateral Pressures. With all the manometers so far described the pressures recorded are the end pressures developed in the artery under investigation. They include, therefore, not only the energy present as lateral pressure due to the stretch on the elastic wall from the increased filling of the vessel, but also the increase in pressure caused by reflection of the wave motion from the obstruction offered by the

cannula. If the true lateral pressure is to be recorded, a cannula of the type ordinarily used, which obstructs the flow in a vessel, must be replaced by a T-shaped cannula with a bore as nearly as possible equal to that of the normal artery; the blood flows straight through the cannula, and the manometer is attached to the side branch. Because the blood washes away anticoagulant from the cannula, clotting occurs rapidly, so the blood should be rendered incoagulable with heparin or some similar agent.

An example of a record so obtained is shown in Fig. 157. In this case the differences between end and lateral diastolic pressures were much greater than those usually present.

It might be thought that obstruction of the carotid artery should give an end pressure in this vessel, but one which corresponds with the lateral pressure in the aorta. To some extent this is true, but not absolutely so, for the carotid artery arises from the curved arch of the aorta, where, owing to centrifugal forces, pressures are not uniform throughout the diameter of the vessel, nor does the carotid artery arise exactly at right angles; in addition, pressure waves are modified in their transmission through the carotid artery with its highly distensible wall. But true lateral pressures in any artery may be recorded by introducing an ordinary cannula through a side branch so that the orifice of the cannula is exactly at right angles to the stream.

The Normal Pressure Levels in the Arteries.—The end mean pressure level, about which fluctuations in pressure occur, is relatively uniform in various animals. Thus Clark[68] finds a value of 100 mm. Hg for the rat, and the values commonly accepted for the rabbit, cat, and dog, anesthetized with ether, are respectively, 90 to 105, 105 to 115, and 110 to 120. The pressure

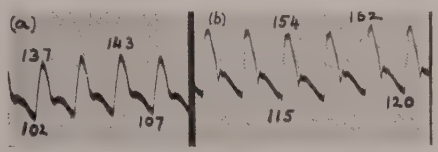


Fig. 157.—Comparison of lateral and end pressures. *a*, shows lateral pressure; *b*, end pressure. Records taken with a Wiggers manometer connected with a T-shaped cannula in the femoral artery of a dog. In *b* a clip was applied to the artery beyond the cannula thus giving end pressures. The numbers indicate systolic and diastolic pressures. Note respiratory variations. (From Bazett and Laplace: Am. J. Physiol. **103**: 48, 1933.)

level seems, therefore, to vary little with weight. Size does exert some effect, however, for the mean pressure is found to be higher in really large animals—it is said to be 155 mm. Hg in the horse. This is to be expected since the pressure must be adequate to overcome any obstructions created by gravity, so that the pressure level is likely to vary more with height than with weight.

Directly Recorded Arterial Pressures in Man Obtained by Arterial Puncture.—There are relatively few reliable data in the literature. The figures obtained by von Bonsdorf,[44] using a Broemser manometer on patients younger than forty and without signs of cardiovascular disease, indicate normal pressures in the brachial artery of 123 systolic and 71 diastolic (usually written 123/71). The mean pressure, when estimated by curve analysis, fell between the limits of 76 and 98. Direct determinations of mean pressure by puncture of the femoral artery and use of a mercury manometer gave values varying from 70 to 95.[211] The subjects were lying down but were not under "basal" conditions. Basal conditions represent those resting conditions under which the subject is exposed to the least stress. To be under conditions which are basal in relation to the circulation, the subject must be in the postabsorptive state (i.e., he must not have eaten for at least six, preferably not for fourteen or more hours), must have been at rest for at least forty-five minutes, must be comfortably

warm, but not warm enough to strain his cooling mechanisms, and he must be relaxed and free from mental worries or any discomfort. The systolic and diastolic pressures given by von Bonsdorf are undoubtedly higher than would be observed in young subjects under basal conditions, and the pulse pressure of 52 is also probably greater. The pressures obtained in man under basal conditions are then somewhat lower than those usually recorded in animals under many anesthetics, including ether. Blood pressures are modified by the pulse rate; accordingly the prevalent habit of stating blood pressure levels without giving the frequency of the pulse should be discouraged.

Indirect Measurement of Arterial Blood Pressure in Man

Since an indirect method without puncture of vessels appears essential for routine clinical work, the principle first suggested by Riva Rocci is of great importance. Measurements are made of the pressure which is required, when applied to a limb, to cause collapse of the artery and obstruct the blood flow. By these methods the various pressures may be measured with as great accuracy as can be attained with the cruder types of manometer and direct exposure of a vessel, but the reliability of the values is below that obtainable by direct puncture and properly used optical recording methods.

Technical Procedures.—The first step is the placing of an armlet or cuff around the upper arm or thigh. The vessels of the forearm and lower leg are sheltered by bones, and are less easily used. The armlet, as was pointed out by von Recklinghausen in 1907, must be broad enough to allow the pressure to be distributed over a large area: For an arm a cuff of 12 to 13 cm. breadth should be used; for a thigh one of 18 to 20 cm. breadth. For children with small arms a narrower cuff (7 cm.) may be used. The cuff is distended with air by means of a pump and the pressure is determined by a mercury manometer or by one of the aneroid pressure gauges which are on the market. It should be checked at intervals against a mercury manometer. Usually the pressure is raised rapidly above the systolic level, and then is allowed to fall slowly while the point of recurrence of the pulse below the cuff is determined. In some instruments air is compressed in a reservoir from which it is allowed to escape into the cuff, so that the pressure can be both raised and dropped slowly. The points at which the pulse disappears and reappears can then be determined and the accuracy of the estimation is improved.

Indices that may be used to detect the peripheral pulse may be grouped into 4 types. The *palpatory* is the simplest, and is that used in the original method: when the cuff pressure exceeds the systolic pressure, the peripheral pulse in the radial or dorsalis pedis artery is obliterated; as the pressure falls the pulse returns, grows to a supernormal amplitude, and then returns to normal. Only the initial return is clearly differentiated, and the systolic pressure so indicated is a pressure some 5 mm. below that indicated by auscultation; the discrepancy may be greater if the observer is inexperienced.

The *auscultatory*, because of its fair accuracy and simplicity, is the method of greatest clinical value. It was originally described by Korotkow. If a stethoscope be held over the brachial artery at the elbow, no sound is heard in the normal subject. But if the pressure be raised in a cuff round the upper arm, particularly if the lower limit of the cuff is close to the position of the stethoscope, sounds will be heard with each pulse, and these disappear as the circulation becomes occluded. If the cuff pressure then be allowed to fall slowly, the sounds heard may be described as falling into 4 phases, though any single subject often fails to provide clear examples of all of them. In the first phase sounds become evident, and the pressure at the occurrence of the first sound is taken as the systolic pressure level; these sounds may be sharp or thudding and not unlike one or other of the heart sounds. If the systolic level is closely approximated and decompression is slow, the respiratory variations of blood pressure may cause a rhythmic disappearance of the sounds in late expiration or early inspiration. In the second phase the sounds become much louder and a hissing murmur may be added to them. In the third phase the sounds consist again mainly of loud thuds. In the fourth phase these thudding sounds gradually fade and become muffled; the fading

may be rapid or very gradual, and in the latter case the effect may be compared with that of a band gradually marching into the distance. This fourth phase ends with a return to silence. Occasionally silent phases may occur between the other phases. Such instances are rare, are not properly understood, but may depend on rhythmical variations in the arterial pressures under investigation. The development of the initial sounds indicates systolic pressure, and probably a pressure which is intermediate between end systolic and lateral systolic pressure. The development of the second phase is associated with the transmission of a much larger pulsation; it is possibly correlated with a pressure within the cuff, which has fallen just below the lateral systolic pressure. The development of the beginning of the fourth phase appears to indicate lateral diastolic pressure, but the values so determined are sometimes deceptive, and often tend to be too low. Such errors are reduced if certain precautions are followed. The auscultatory systolic criterion is always found at pressures some mm. above the palpatory if the stethoscope is properly situated close to the point of compression of the brachial artery by the cuff; if this pressure difference is not found, it indicates that either the stethoscope is inaccurately placed, or that the brachial artery is abnormally situated so that the auscultatory readings are unreliable; occasionally merely changing the cuff to the opposite arm will give quite different and more reliable pressure readings. In making readings by auscultation or any other method, several inflations and deflations should be made before readings are recorded, for even with experienced subjects an initial alteration of blood pressure from excitement, in response to the sensations of circulatory obstruction, is the rule. Deflation should be carried out slowly, for rapid deflation alters the circulation by allowing the upper vessels to discharge suddenly into empty arteries below the cuff, and abnormally low diastolic readings result. Pressure within the cuff should be released between readings, and not be maintained longer than necessary, since any congestion, not only causes the subject discomfort and may induce reflex changes, but also, through overdistention of the vessels below the cuff, may modify the flow in the brachial artery and cause estimates which are too high. Errors from this source are less than those which are due to rapid decompression. The stethoscope bell should be applied to the elbow as lightly as possible; if applied forcibly it may itself compress and distort the vessel and give rise to sounds. This is especially likely to happen when the diastolic pressure is low, for a pressure of 130 grams applied to a bell of 2 cm. diameter is the equivalent of more than 30 mm. Hg pressure. In many cases in the literature sounds have been recorded as continuing without fading down to "zero" pressure and diastolic pressure has been estimated as zero. It is certain that in animals the lowest diastolic pressures ever recorded are always well above the atmospheric level, so that these low estimates of diastolic pressure must be considered as erroneous. In some cases at least they depend on failure to observe the above (particularly the last) precautions, though sounds may sometimes be generated in vessels in the absence of compression. A standardized technique is described by a Committee of the American Heart Association.[256]

The oscillatory criteria were developed particularly by Erlanger[102] and Erlanger and Hooker.[104] They form the basis of the Pachon and Plesch methods commonly used in France and Germany, respectively, as well as that of the recording Tycos instrument. The principle depends on the visual or graphic estimation of the pulsations transmitted by the compressed artery to the manometer. When the cuff pressure exceeds systolic pressure, small oscillations are transmitted with each pulse to the manometer as the result of the impact of each pulse against the upper edge of the cuff. As the pressure is lowered and the pulse passes beneath the cuff, these pulsations show a sudden increase in size and duration, and this change indicates systolic pressure. As the pressure is lowered still further, the pulsations increase in amplitude, and are considered to reach their maximum, according to the Pachon school, when the compression pressure equals mean pressure. But this conclusion is open to question and, in any case, the point of maximum amplitude is often ill-defined. The pulsations remain large, as the pressure is lowered further, and then suddenly show a rapid diminution in size; the commencement of this change is said to indicate the diastolic pressure level. The size of the pulsations cannot be accurately estimated on a mercury manometer, since any change in pulse rate will cause an alteration in the size of the oscillation, even if the pressure changes are unaltered. Even with an aneroid manometer the fluctuations are small. The pulsations may be exaggerated by using a differential capsule. A tambour covered with a delicate highly sensitive membrane is employed, and both sides of this membrane are connected with the cuff and compression system; in this way the membrane is protected from damage by the high pressures, since they are applied to both sides. But of the two connections with the

cuff, one is free and able readily to conduct pulsatile changes, the other is constricted and the obstruction damps any sudden pressure changes, so that the membrane responds to sudden pulsatile changes by movements in a single direction.* These various modifications usually provide clear indices for systolic pressure but the values obtained are higher than those obtained by auscultation, and the differences probably vary somewhat with the type of instrument as well as with the individual subject and the character of the pulse curve. The higher values obtained with such instruments probably represent end systolic pressures. The diastolic criterion is less definite, for spontaneous variations in the size of the pulse are seen with respiration, particularly when the pulse rate is not constant, so that the size of oscillation is not solely dependent on cuff pressure. As respiratory variations in diastolic pressure also occur, it may be quite impossible to determine with any accuracy where any sudden change develops.

The *"formo-oszillatorisch" criteria* suggested by von Recklinghausen[252] depend on the use of a type of instrument similar to that used for oscillatory methods in general, but the natural frequency of the system is improved to allow a study of the shape, rather than of the mere size, of the pulsations. Here then a recording system becomes essential, but

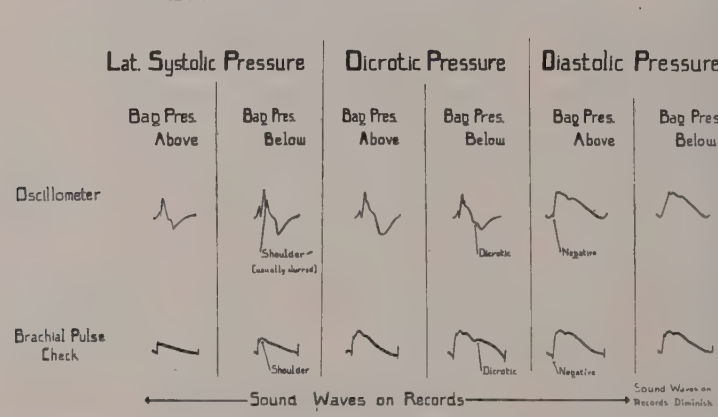


Fig. 158.—The criteria for "lateral" systolic, dicrotic, and diastolic pressures obtained oscillometrically are indicated diagrammatically according to the shapes of the recorded curves. Throughout the range where brachial pulsations occur fine waves associated with sounds develop just after the sharp upstroke until the diastolic pressure is reached, when they gradually fade. These are too small to be visible on this diagram.

the method allows the differentiation of end from lateral systolic pressure, more certain estimation of diastolic pressure, and also a possibility of estimating the pressure of the dicrotic wave.

A modification of von Recklinghausen's method, devised by Bazett and Laplace,[34] uses optical registration and includes also an optical study of the shape of the pulsations of the brachial pulse below the cuff. By utilizing in the cuff a system of 3 bags, one on top of the other, of which the smallest and innermost is used merely as a tambour, the natural frequency of the system is improved. End systolic pressures are indicated by the changes in size of the oscillation already described, and the lateral systolic pressure by a larger and more sustained wave in both the oscillogram and peripheral pulse. At pressures above lateral diastolic pressure an initial sharp negative wave is developed in the peripheral pulse, a wave demonstrated by Erlanger[103] and attributed by Bramwell to formation of "breakers" (like those developing from waves on a seashore). This negative wave, particularly when used

*In some forms, as in the Tycos instrument, a double compression cuff is used; the upper cuff connects with the damped obstructed side of the membrane, the lower with the free side; pulsations hitting the upper edge of the upper cuff then produce small inverted pulsations, but passage of the impulse through to the lower cuff produces a reversal to a larger upright wave.

in conjunction with the shape of the oscillogram, the upstroke of which becomes less abrupt when the pressure ceases to exceed diastolic pressure, gives a sharp indication of diastolic pressure (Fig. 158). As in von Recklinghausen's system the pressure of the dicrotic wave may also be determined.

A highly sensitive oscillometric method, but one which does not lend itself to any determination of the shape of the pulse curve, has also been described by Wishart.[321]

Relative Value of the Various Criteria.—It is probable that the auscultatory method is still the method of choice for clinical use, though the "formo-oszillatorisch" methods are almost certainly much more accurate and reliable. However, such increases in accuracy do not justify the difficulties added by the use of complicated recording methods, particularly optical methods, unless the greater accuracy gives information that can be used. By mathematical analysis of such data, deductions have been made by Bazett and his co-workers[33] as to the cardiac output; such deductions appear to be applicable to clinical material. If such deductions prove to be justified, then, and then only, will the more complex methods assume importance in clinical work.

Causation of the Criteria.—The *auscultatory* criteria depend on the generation of vibrations when the compressed segment of artery is suddenly distended, and when a stream of blood is suddenly forced down it into the dilated artery with stagnant blood below. The murmur character is probably contributed by the eddies generated in the fluid.

The *oscillatory* changes are complex.[35] When the compressing cuff is at a pressure exceeding systolic pressure, the artery is collapsed, and the collapsed segment has conical junctions with the uncompressed sections. The upper cone is stretched and enlarged with each pulse beat, and these changes transmit pulsations to the cuff. As the compression pressure is allowed to fall, the cone is distended more and more widely and affects the cuff system to a greater extent, until ultimately the cone closes in diastole behind a small column of fluid, which passes down the compressed segment as a sort of bolus. This is associated with a marked increase in the oscillogram and with the first pulse (but a very small one) below the compression. The energy distending the cone is derived both from the lateral pressure and from kinetic energy; the cuff pressure is slightly below end pressure. When the cuff pressure is reduced to the lateral systolic level, the whole length of the compressed segment is able to be momentarily open; this is associated with a much larger pulsation (and generation of much louder sounds). The oscillogram grows much larger. At this and slightly lower pressures the wall of the artery undergoes rapid changes in state; in the systolic phase the artery may be distended (internal tension greater than that in the cuff), in the intermediate phase the wall may be floating free (internal and external pressures equal) and in diastole the lumen may be collapsed. The oscillations are of considerable volume, and the vibrations complicated. The pulse wave is transmitted very slowly at its start (wall floating free) and more rapidly later when the wall is under tension. The foot of the wave is transmitted more slowly than the peak, the wave grows in steepness as it travels, and may fall over like a breaker on the shore to create an initial negative wave. In this intermediate stage the vessel below the cuff is distended normally at systolic pressure, but is disconnected from the central vessels before diastolic pressure is reached. This gives it a longer time interval in which to empty itself into the capillaries, and the pulse pressure peripheral to the compression therefore may be larger than that existing central to the cuff.

Claims have been made that the oscillations of maximum amplitude occur when the cuff is distended at a pressure equal to the mean pressure. The accuracy of these claims is doubtful. Mean pressure may be estimated in man by graphic integration of a recorded pulse curve, after assigning to its peaks and troughs the values obtained for systolic and diastolic pressure.

Indirect Estimates of Pressures in Man.—The values considered normal vary somewhat with the method used for determination. This probably depends on the confusion resulting from failure to distinguish between end and lateral pressures. Most of the values obtained by oscillatory methods given in the literature probably indicate end pressures. The values determined by auscultation are lower, particularly the systolic estimates, yet even these estimates are likely to be a few millimeters above the lateral systolic pressure.[33] No statistics are yet available for lateral systolic pressures as estimated according

to von Recklinghausen's principles, nor for the effect of age, etc., upon them. Under basal conditions, they appear to be some 10 to 20 mm. below end systolic pressures and 5 mm. below the auscultatory estimates.

The normal pressure levels found in a young human subject *under basal conditions* may be considered commonly to approximate the following values (they may cover a still wider range):

Systolic pressure, 100 to 120 mm. Hg

Diastolic pressure, 65 to 80 mm. Hg

Pulse pressure, 35 to 40 mm. Hg

Mean pressure = diastolic pressure + ⅓ to ½ pulse pressure, or about 77 to 100 mm. Hg.

Such values are obtained by ordinary clinical methods; they lie between true lateral and true end pressures. Lateral pressures may be insignificantly lower except in the case of systolic and pulse pressures which may be 5 to 10 mm. below these figures.

The normal auscultatory values for men at various ages, when measured with the subject sitting under conditions such as those of the doctor's office, are indicated in Fig. 159, which indicates the average values for pulse rate, systolic and diastolic pressures at various ages. In the age limits between 16 and 65 normal blood pressure limits are expressed according to the average values observed by Symonds[294] on individuals in his highest and lowest weight groups. It will be noticed how marked a contrast is observed in the pressures. Pulse rates are also definitely somewhat slower (some 4 or 5 beats) in larger individuals, though this is not indicated in the graph. Data obtained by Cadbury[61] on Chinese students are also indicated for comparison; the slightly higher pulse rates recorded are explicable on the probable lower average weight, but the low blood pressures are evidently not explicable on any such grounds. Similar low pressures have been recorded in Bombay Indians. Racial factors are probably involved. To some extent climatic conditions may play a part, in that the pressures recorded in the tropics from Europeans and Americans are usually subnormal, particularly if the individual has made an extended stay in the tropics, but even so the pressures recorded are usually considerably higher than those observed in native subjects. The pressures recorded in American negroes show no significant differences from those recorded in white subjects. Values observed in women between puberty and 40 years of age are usually some 7 mm. lower than those found in men. The carefully analyzed data of Stocks and Karn[292] on English boys give curves very similar to those of Fig. 159, but show a more abrupt change with age and more sudden changes at the age of puberty.

Too great emphasis should not be placed on blood pressure levels which differ somewhat from average values, for considerable variations are observed even in a single individual. There is normally a considerable rise in systolic and often a slight fall in diastolic pressure after meals, and blood pressure values obtained in a strictly basal state, with the subject lying down, are probably at least 10 to 20 mm. lower than those indicated in Fig. 159; also under basal conditions the pulse pressure and pulse rate may both be decreased.[8] There is a tendency among physicians to call any systolic pressure below 100 mm. in an adult abnormal. As far as this applies to the somewhat excited state of an individual in a doctor's office this may be justifiable. Under the more normal condi-

tions of a laboratory with repeated examinations of a subject, in the absence of all excitement and particularly with the room warm, auscultatory systolic values of 95 are not uncommon and values of 90 not necessarily abnormal in the young subject even in the sitting position. Similarly systolic pressures above 140 mm. in a subject of twenty years of age do not always indicate anything more serious than a labile vasomotor system and a general excitability. Sometimes, if an

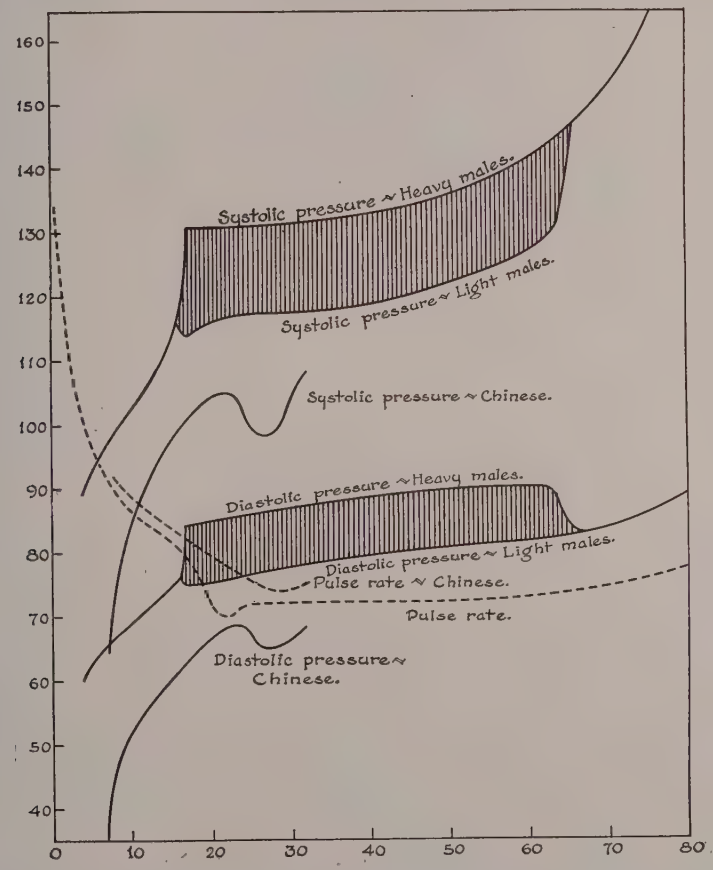


Fig. 159.—A composite graph representing normal variations in blood pressure and pulse rate with age. Abscissae, age in years. Ordinates, arterial pressure in mm. Hg and pulse rate (mean values) in beats per minute. The blood pressure curves represent the data of Faber and James, of Symonds and of Bowes with Symonds' data separated according to the extremes of the weight range. Data are not available for a similar differentiation in other age groups. The pulse rate curves represent the values obtained by Faber and James and by Volkmann (American and German subjects) and by Cadbury (Chinese subjects).

examination is repeated at intervals for fifteen minutes or more until the subject is bored, such pressures fall to normal levels. The normal values for the subject lying down are somewhat lower, for the subject standing somewhat higher, than those found in the sitting posture.

Little is known of the normal values of mean pressure in man. Values of 70 to 98 obtained by direct puncture have been quoted. Graphic integration of optical pulse curves after assignment of values for lateral systolic and diastolic pressures determined indirectly has given average values for mean pressure of 79 and 87 mm., respectively, for subjects under and over forty years of age, when they were lying down under basal conditions. When standing or sitting the respective averages were 97 and 102 mm.[33]

THE PRESSURE PULSE IN THE ARTERIES

The central pulse in the aorta has already been briefly described (page 377), and an optical record of such a pulse has been reproduced (Fig. 133). The characteristics of the central pulse are (1) a sudden rise as the aortic valves open; (2) a systolic period when the pressure may remain at a plateau, rise gradually or fall rather steeply (as in Fig. 133); (3) a sudden fall (the incisura) as ejection ceases; (4) rapid vibrations (the after-vibrations) as the valves close; (5) a later more prolonged positive wave (the dicrotic wave); and (6) a gradual diastolic fall of pressure until the commencement of the next wave. The period of sudden rise of pressure (period 1) is commonly modified by one or more rapid vibrations on the upstroke, probably caused by the sudden tension of the aortic walls. The second period comprises the remaining time during which blood is being ejected. The pulse curve is said to be "anacrotic" if the general pressure level rises, "catacrotic" if it falls. The change in level depends on the balance between the rate of ejection on the one hand, and the rate at which blood leaves the aorta for the small vessels on the other. It is also much modified by the conditions for reflection of waves. Reflections of the primary pulse wave cause secondary waves to appear in the central pulse; these are known as predicrotic waves. The origin of the incisura and after-vibrations has been mentioned in relation to the heart. The former depends on the momentum of the ejected fluid, the latter on valve vibrations which occur as retrograde flow follows the incisura and closes the valves. The reflection of this closing wave gives rise to the later dicrotic wave. Reflected waves also continue to return from the periphery and not uncommonly they fuse with a true dicrotic wave of central origin to form an apparent but impure "dicrotic" wave in the central arteries. Similar smaller reflected waves are also seen as postdicrotic waves. Immediately preceding the next arterial pulse small waves may be seen in the central pulse; they are caused by thrusts transmitted to the aorta from the heart. A small positive wave may thus be caused by auricular contraction and either a positive or a negative wave by isometric ventricular contraction.

The peripheral pulse is very different in shape (see Fig. 161). Following the steep upstroke of the pulse wave the systolic phase is usually "catacrotic"; the incisura may be represented by a more or less slurred dip which is often followed by a quite definite dicrotic wave. These waves, though labelled dicrotic, are only partly of central origin. Usually the time relations of the dicrotic wave suggest the presence of a wave of central origin. It is, however, undoubtedly much modified by fusion with reflected waves. The small vibrations of higher frequency seen in the central pulse become extinguished in the transmission of the wave through the elastic vessels.

The part played by reflected waves in modifying the shape of the pulse curves may be seen in considering the pressure curves recorded at different distances from the heart.

Arterial Pressures in Different Vessels.—When the rate of blood flow is relatively slow, as it is with an individual at rest, there is little frictional loss of free energy within the larger central arteries. Kinetic energy then plays a subsidiary role, and consequently mean pressures are almost identical in all the larger arteries, provided that the subject is lying down, so that the effects of gravity are small. The pressure curves at different points are by no means identical, however, and systolic pressure levels (and pulse pressures) may differ considerably. These major differences depend on the undulatory phenomena imposed by the intermittent ejection of blood into a highly distensible elastic system. They depend on reflected waves and a consequent difference in the temporal distribution of energy according to the conditions under which the primary and reflected waves fuse. This may be seen in the curves of Fig.

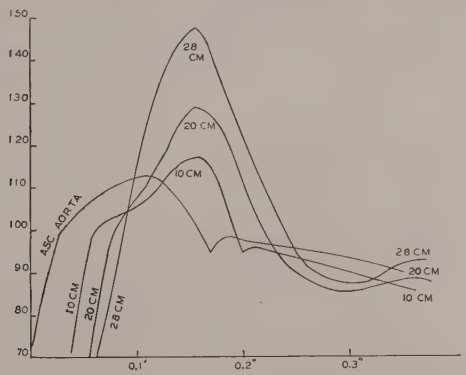


Fig. 160.—Reconstructions of aortic pressures (redrawn after Hamilton and Dow[159]) from records taken at various distances (expressed in centimeters) from the arch of the aorta in dogs. The pressure gradients existing between different points in the vessel at any given stage of the cycle may be deduced from the records. The abscissae indicate time in seconds, the ordinates pressures in mm. Hg.

160, which represent the pressures observed in the aorta of a dog at various distances from the heart. The flat plateau-like curve observed in the ascending aorta consists of a primary wave onto which a reflected wave is fused after 0.1 second; the reflected wave consequently fuses with the descending limb of the primary wave. At a distance of 28 cm. from the heart the primary wave starts much later (over 0.06 sec.) and the reflected wave (since it is near its point of reflection) now fuses with the end of the ascending limb of the primary wave. A peaklike wave of high systolic pressure is consequently developed. Though the systolic pressures may in this way differ considerably as indicated in Fig. 160, the peaklike waves are of shorter duration. The curves are also different in their diastolic phases; the level reached may be lower, or a low pressure may be attained more rapidly, so that the period of low pressure is lengthened. Consequently, the mean pressures are almost identical, in spite of the great differences in systolic pressures.

The fact that the mean pressures are not completely identical depends on the interaction of frictional losses and on initial differences in free energy due to the directional character of kinetic energy. If the flow be hindered this kinetic energy is transformed to pressure. Volkmann[301] in 1850 showed that the mean end pressure in the femoral artery commonly exceeded that in the carotid by 2 to 30 per cent. Bazett[32] demonstrated that the free energy is slightly higher in the femoral; when the carotid and femoral arteries are joined, blood usually flows slowly from the femoral to the carotid. This occurs more readily if the left carotid is used, because at the origin of this vessel the stream has been deflected around the aortic arch; the kinetic energy of the stream is directed towards the femoral arteries.

The combined effects of the variations in total free energy and in the time relations of its distribution may be illustrated by records obtained in man (Fig. 161). The subject in question had hypertension and consequently the pressure levels are abnormally high and the rate of wave transmission is also

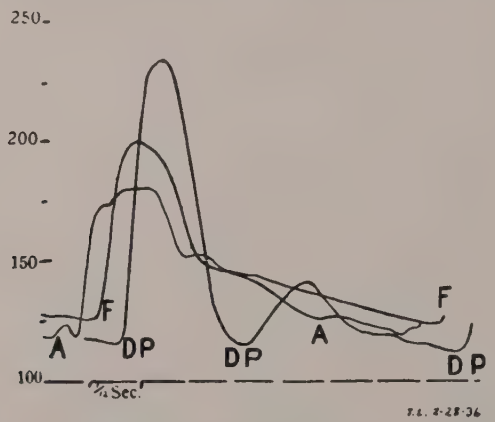


Fig. 161.—Simultaneous direct arterial pressure readings in the axillary (*A*), femoral (*F*), and dorsalis pedis (*DP*) in man (hypertensive subject). (From Hamilton, Woodbury, and Harper: J. A. M. A. 107: 856, 1936).

above normal, but the records serve to illustrate the general relationships of the pressure curves to one another. The values recorded are axillary 165/120, femoral 200/124, and dorsalis pedis 235/116. Graphic integration of these curves, however, shows mean pressures for the axillary of 146, for the femoral of 148, and for the dorsalis pedis of 143 in spite of the great differences in systolic pressure. The slight differences in mean pressure would be explicable through the transmission of greater kinetic energy to the femoral than to the axillary with later conversion of this energy into pressure energy, together with loss of some free energy through friction between the femoral artery and dorsalis pedis.

The differences which exist between the pressures in the femoral and carotid arteries of animals are of interest in connection with the fact that similar differences may be demonstrated between the pressures in the arm and thigh in man. These differences are exaggerated in certain clinical conditions, namely,

aortic regurgitation, some cases of arteriovenous aneurysm, hyperthyroidism and anemia, as well as in the normal individual after exercise. All these conditions are associated with an increased velocity of flow and increased pulse pressure. Increased pulse pressure per se is not necessarily effective, for the differences are not consistently increased in cases of arteriosclerosis. Differences in the local condition of the arterial wall in different areas modify the local development of the pulse wave, but are not normally responsible for the differences encountered in the clinic.[139, 227]

The differences in pressures recorded from the carotid and femoral arteries may be modified experimentally. They may be augmented not only by the production of aortic regurgitation or arteriovenous aneurysms, but also by administration of adrenalin. They are reduced by histamine, acetylcholine, or by painting the aortic wall with cocaine.[32, 185] It is questionable whether such differences should be measured on an absolute basis, or in proportion to the pulse pressure. In any case the factors concerned are likely to be mainly physical and it is improbable that contraction of peripheral vessels exerts any propulsive force on the blood, for contractions of adequate rapidity have not been demonstrated, and the volume changes in a vessel parallel those in internal pressure.[118] The emission of sympathetic nerve impulses to the peripheral vessels with rhythms which vary, not only with respiration, but also with the pulse cycle,[52] makes it possible that the distensibility of the large vessels may vary during a cycle.

If the individual assumes a vertical posture, differences in the pressures within different vessels are also created by the effects of gravity. The pressures in the vessels in the head are reduced while those in the legs and feet are increased in proportion to the intervening columns of blood. In a man of average size the arterial pressures (systolic, diastolic, and mean) at the level of the base of the skull are reduced some 15 mm. Hg below those in the aortic arch, while the pressures in the dorsalis pedis are increased by about 100 mm. Hg.

Wave Transmission in the Arterial System.—If the subject is lying down, gravity effects may be considered negligible, and the other forms of free energy tend to reach an equal distribution in the arterial tree. The transmission of pressure proceeds, however, relatively slowly in such a highly distensible system (some 3 meters a second in the central vessels and 7 to 14 in the more peripheral). Any equalization of pressures, therefore, is only slowly attained and is preceded by complex wave phenomena. Pressure energy tends to spread in all directions, but kinetic energy is unidirectional.

The complex pulsatile waves generated by the intermittent expulsion of blood are transmitted through the whole system. These waves travel much more rapidly than the blood itself (compare the rate of transmission of the pressure impulse in a series of billiard balls with the actual rate of movement of the column as a whole). The pressure waves affect the column and develop an accelerated motion within it. In the circulation, pressure waves and velocity waves proceed in close association so that the whole arterial column is set into more rapid motion, though the velocity is not uniform throughout.

Pulse Wave Velocity.—The rate of transmission of the front of the pulse wave may be utilized to determine the volume elasticity coefficient of the vessels, but values so determined are somewhat arbitrary. It has been clearly demonstrated that the rate of wave transmission is much slower in the larger than in the smaller more peripheral vessels, so that in any section the velocity is not constant but is steadily increasing. For effective calculation it is, therefore, the

integral that should be used; but such integration is impractical, in view of the physiological variability of the contraction of the wall. The length of any vessel is not accurately determinable, and itself varies with posture; any measurement of tortuous vessels is still more inaccurate. Measurements of wave velocity must, therefore, be considered arbitrary values, only comparable with one another, if the points of pulse registration and methods of measurement are identical. Wave velocities estimated for subjects of different ages under basal conditions are shown in Table XV. More numerous data on the more peripheral

TABLE XV

PULSE WAVE VELOCITY IN DIFFERENT VESSELS IN MAN (FROM BAZETT ET AL.[33])

(Values in Meters per Second)

	HEART TO SUBCLAVIAN		SUBCLAVIAN TO FEMORAL		SUBCLAVIAN TO BRACHIAL		FEMORAL TO DORSALIS PEDIS	
	LYING	STANDING OR SITTING	LYING	STANDING OR SITTING	LYING	STANDING OR SITTING	LYING	STANDING OR SITTING
8 subjects mean age 27 (21-33)	3.26	3.00	5.90	7.27	5.73	7.09	8.78	13.74
4 subjects mean age 51 (43-63)	3.27	3.22	7.62	10.41	6.90	8.71	13.05	13.60
1 subject age 76	5.60	–	11.70	–	7.40	–	13.70	–

vessels reported by Hallock[153] demonstrate the marked effect of age on the speed of transmission in these vessels. The few data available seem to indicate that this increased rate of transmission develops later in the larger central vessels, where the main reservoir function is located. This is due to an initial compensation by a change in cross-sectional area which secondarily affects the distensibility.

In the large central vessels the above-mentioned compensation is probably achieved either by an increase in the ratio of the diameter to the thickness of the vessel wall or else through variations in the contraction of the muscular coat. The large central vessels cannot be regarded as simple elastic tubes; the characteristics of their walls appear to vary even in young individuals. The muscular layers are considerable and no doubt have important functions. Hürthle found that one-third to one-half of the aortic wall consists of muscular tissue. The data in Table XV show that, whereas the standing posture might be expected on physical grounds to cause an increase in the wave velocity in the ascending aorta (since the blood pressure is usually increased and the vessel should be less distensible) actually the opposite change is seen when the subject stands. It has been found that the pulse-wave velocity in the large central vessels tends to show changes opposite in sign to those in the peripheral vessels. When the latter are dilated and exert a reservoir action, the wave velocity in the central vessels is relatively high and these are presumably constricted. When, on the other hand, the peripheral vessels are constricted, the central vessels appear to carry a larger proportion of the reservoir action. The marked enlargement of the central vessels with advancing age also implies that as the peripheral vessels get less distensible (as indicated by their increased wave velocities), a larger and larger proportion of the reservoir action is carried by the central vessels. In order to obtain any idea of the magnitude of this reservoir action, the diastolic volumes of the various vessels must be known. More or less arbitrary values, which appear to give an estimate of the reservoir action, have been assigned to these.[33]

The rate of wave transmission is such that under all normal conditions the wave travels the whole length of the vessels and reaches the smaller most peripheral vessels, such as the

dorsalis pedis artery, before the closure of the aortic valves. This may be seen in Fig. 162. As a consequence, the whole arterial tree, and not a mere part of it, is distended during systole; probably this condition is regulated by vascular reflexes, for it holds true whether one is dealing with a small or a large individual, with a slow pulse of 40 and an expulsion period of about 0.45 or with a fast pulse of 130 and an expulsion period of about 0.25, with peripheral vessels constricted by cold or dilated by exposure to heat. The necessity of distending the whole arterial tree to attain efficiency may be a factor in determining the slow pulse of large animals. (The normal resting pulse rate of the elephant is 28 beats per minute.)

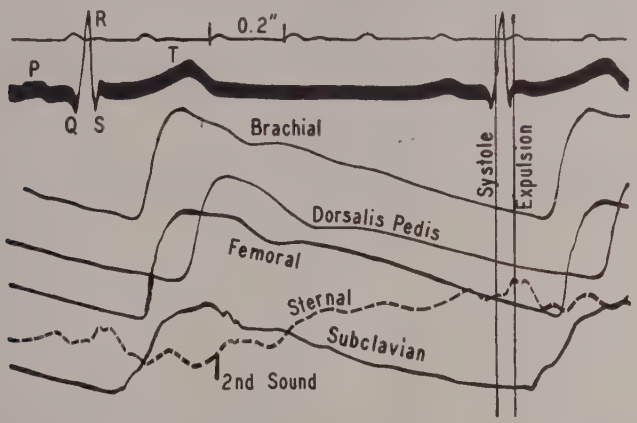


Fig. 162.—Pulse tracings from different arteries, electrocardiogram (top) and record of anteroposterior movements of the sternum (sternal). Human subject. Note delay in peripheral vessels. The upstroke in the dorsalis pedis begins before the second heart sound. The lines marked systole and expulsion indicate, respectively, the probable commencement of detectable changes in intraventricular pressure (ventricular contraction) and the opening of the aortic valves. The sternal record is shown by a dotted line.

VELOCITY OF FLOW IN THE ARTERIES

The pressure wave travels rapidly (2 to 20 meters a second) and, as it progresses, produces an acceleration of blood along the whole arterial tree. The actual movement of fluid so produced is much slower. It has already been pointed out (page 335) that the mean velocity is about 20 cm. a second in the aorta and that it is very close to this figure in the larger arteries where the stream bed is little altered. Actual measurements of mean velocity in animals have given values of 18 cm. a second in the abdominal aorta (Broemser[51]) and of 14 to 15 cm. in the carotid and femoral arteries (Machella[226]). The velocity of flow in any artery is far from uniform; at the peaks of the systolic waves it is of course much greater than during the diastolic portion of the pressure curve. The figures just given for the mean velocities indicate that blood takes 7 seconds or more to reach the most distant arterioles of the foot. This may be contrasted with the time of 0.2 to 0.3 second taken for the change in pressure to be transmitted (see Fig. 162).

The distensibility of the arterial tree modifies the rate of flow just as it does the pressure. Flow at the root of the aorta is obviously purely systolic except for the slight diastolic flow due to the distensibility of the semilunar valves and of the origin of the aorta. More peripherally the flow may continue

uninterruptedly since the central vessels can act as reservoirs supplying blood. Under conditions of rest, when the rate of flow is low and kinetic energy does not play a large role, the movement of blood is largely determined by the pressure changes. When pressure is raised peripherally as the result of wave reflection it causes a temporary excess of free energy in the periphery and a temporary retrograde flow. The presence of such a retrograde flow has been recently demonstrated by records of the volume changes in peripheral areas (plethysmograms). The volume has been found to rise to a maximum at the peak of the pulse wave and then to retrogress at a rate faster than can be accounted for by flow into the veins. Some retrograde flow back into the central arteries must have occurred.[326] The magnitude and duration of such retrograde flows under normal conditions are subjects of controversy. One must conclude, however, that the velocity of flow varies at different stages of the cycle, that even at low cardiac outputs it may attain a magnitude at the peak of the pressure wave of nearly one meter a second or more, and that retrograde flow may occur both in the more central and more peripheral vessels. The normal flows associated with various conditions are not exactly known.

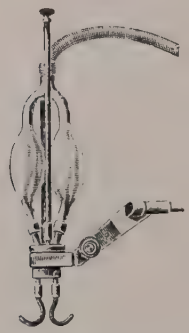


Fig. 163.

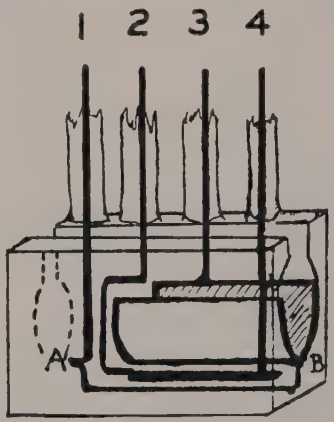


Fig. 164.

Fig. 163.—Ludwig's stromuhr The tubes on the lower end of each of the two glass bulbs pierce a circular brass platform and end flush with its surface. This platform pivots at its center on a similar lower platform with two openings connected with the tubes that lead to the blood vessel.

Fig. 164.—Thermo-stromuhr. Direct current entering by leads 2 and 4 passes through a resistance unit. A silver plate conducts the heat to the artery. An E. M. F. develops which is recorded on a galvanometer or potentiometer through leads *1* and *3*. *A* is the cold junction which has a temperature determined by that of the entering blood; *B* measures the temperature of the silver plate. The more rapid the blood flow the less the plate is warmed. (From Schmidt and Walker: Proc. Soc. Exper. Biol. and Med. 33: 346, 1935.)

Measurement of Velocity of Flow in Peripheral Vessels.—Instruments used for such measurements belong to two main types: (a) those that measure volume flow and (b) those that measure velocity. If either of these values be known, the other may be calculated, provided that the cross-sectional area of the vessel can be determined. To instruments of type (a) belong Ludwig's historic stromuhr which collects blood in a vessel and then returns it again to the vascular system. By rotating the glass bulbs either bulb may be filled with blood, while that collected in the other is driven back into the vessel (Fig. 163). The second bulb is filled with oil. The flow from a vein may be collected for a brief period in a graduated tube, measured, and later returned to the circulation. Our knowledge of circulatory changes

has been much advanced by Rein's development of a thermo-stromuhr for measurement of volume flow.[253] This method depends on the heating of the blood in the vessel by the passage of a high frequency electric current across it. Two thermocouples, one at each end, measure the degree of heating of the stream, which is less the greater the flow. The instrument fits about the vessel and so does not disturb the circulation. It is standardized empirically, but, since the thermocouples are outside the vessel, the values obtained are apt to vary with the accuracy of fit. A modified form utilizing direct current from a battery has been described[278] (see Fig. 164).

Instruments of type (b) include (1) those which measure differences in pressure created by kinetic energy. In these two tubes connected with a differential manometer face in opposite directions, one upstream and the other downstream. These are known as Pitot's tubes. Another type (2) measures by a differential manometer the fall in lateral pressure resulting from flow through a constriction; this, known as the Venturi meter, depends on the conversion of pressure into kinetic energy. The second type of instrument can be applied without the use of anticoagulants,[51, 304] since vessels can be constricted from without. The thermal principle has also been applied (3) by the use of an electrically heated thermocouple needle introduced directly into the blood stream,[137] or (4) by the introduction of a fine resistance wire into the vessel.[226] In the latter a wire, forming one arm of a Kelvin bridge, is heated electrically. Any increase in velocity cools the wire and alters its resistance; there is little lag and little or no interference with the circulation. The curves of Fig. 165 were obtained by this method.

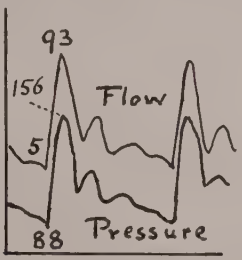


Fig. 165.—Simultaneous records of velocity (above) and of pressure (below) in the femoral artery of a dog. The numbers, 93 and 5, represent the maximum and minimum velocities in the artery in centimeters per second, and 156 and 88, the corresponding maximum and minimum pressures. (Redrawn from Machella: Am. J. Physiol. 115: 632, 1936.)

All these methods are valuable in investigating the flow through individual organs, but for measurement of the velocities in the aorta itself they have deficiencies. The mechanical methods interfere with the circulation and tend to limit movements of the heart and to decrease cardiac efficiency; the Rein method cannot follow rapid fluctuations, and the hot-wire method fails to differentiate between flows in different directions.

Velocity Curves in the Large Arteries.—The curves obtained by different methods differ; these differences are to some extent merely apparent. Neither the Broemser (analysis of pressure changes at a constriction) nor the hot-wire method gives curves which are lineally related to the velocities; in the former the lower velocities are minimized and in the latter exaggerated. Consequently, in Fig. 166, two of Broemser's curves[51] have been redrawn on a linear scale, as well as the hot-wire record of femoral flow shown in Fig. 165. Each has been given the same arbitrary duration for a pulse cycle. In all (ascending aorta, abdominal aorta, and femoral) the peak of systolic flow far exceeds that during the rest of the cycle; it reaches 90 to 160 cm. per second. The mean velocity (with the exception of the probably aberrant curve 2) is around 20 cm. per second. According to Broemser's curves the incisura may be accompanied by a retrograde velocity amounting to over 20 cm. per second even in the abdominal aorta. According to curves obtained by the hot-wire method the notch preceding the dicrotic wave in the femoral (appearing earlier in the cycle since the pulse rate was much slower) is associated with no increased velocity of any sort. Broemser's curves have been criticized on theoretical grounds by O. Frank; the intensity of any retrograde flow, and the distance it extends in the vascular system must for the present remain an open question.

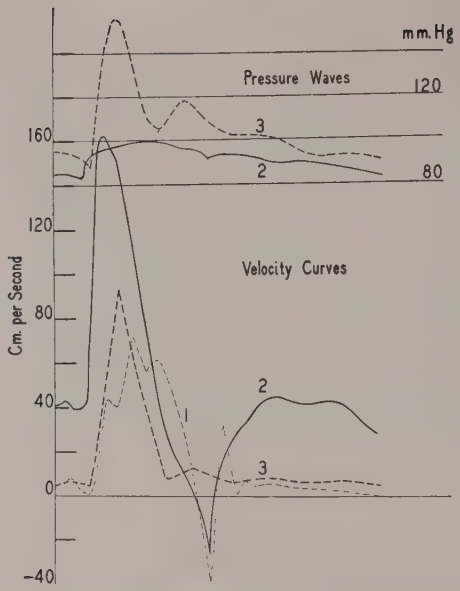


Fig. 166.—Velocity of blood flow in arteries. Curves reduced to a linear scale. *1*, velocity in ascending aorta; *2*, in the abdominal aorta (from Broemser's data); *3*, in the femoral artery (from Machella's data). The upper curves represent the pressures recorded simultaneously with curves *2* and *3*. The time scale is arbitrary and represents a single pulse cycle.

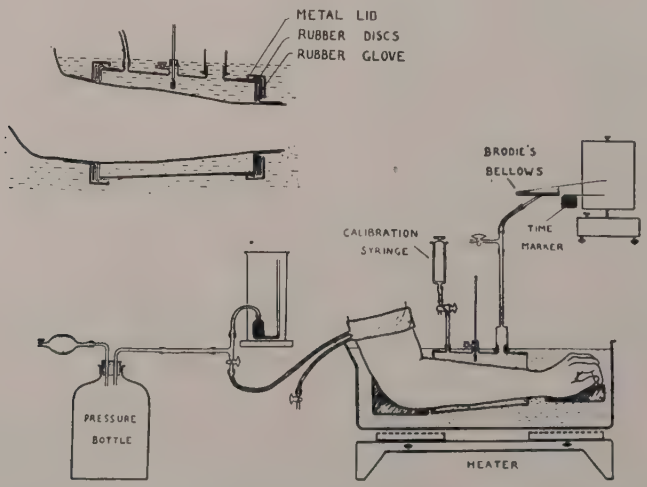


Fig. 167.—Plethysmographic method of measuring blood flow in the arm. The forearm is in the plethysmograph which lies within a water-bath (to maintain an even temperature). The pressure bottle serves to inflate the armlet and so to block venous return when desired. Volume changes are recorded by the bellows recorder. (From Prinzmetal and Wilson: J. Clin. Investigation 15: 63, 1935.)

It may be noted that the pulse pressure recorded in Broemser's curve 2 was only 17 mm., and the pulse rate was 205; the condition of the circulation was, therefore, certainly abnormal.

Measurement of the Volume Flow in a Limb.—One of the simplest and most generally used methods for determining the flow in a limb depends on the swelling of the limb from inflow of blood when the venous outflow is suddenly blocked. The venous outflow is blocked by a Riva Rocci armlet which is distended to a pressure considerably in excess of venous and considerably below arterial pressure. The limb is encased in a plethysmograph and the rate of increase in volume in the first few seconds after the obstruction of the vein is measured. The record can be standardized by the injection into the system of a known volume with a syringe. A modification of this method is illustrated in Fig. 167. Here the plethysmograph is immersed in a bath the temperature of which can be maintained constant.[129, 217, 250] Even so the circulation through the limb may be modified reflexly by the temperature to which the rest of the body is exposed.

QUANTITATIVE CONSIDERATIONS OF ARTERIAL PRESSURE

It will be obvious to the reader that our knowledge of the circulation would be much enhanced if the relations of pressure to flow could be expressed in mathematical terms. Attempts to approach such a solution have been made repeatedly during the last fifty years, but the complexity of the circulatory system makes even empirical solutions unreliable. For the most part the system has been treated in a simplified schematic way by utilizing average values and neglecting the complexities introduced by fluctuations in pressure and velocity. Resistance to flow has been considered as constant throughout the cardiac cycle, and flow has been considered merely in terms of the mean rate of flow. These simplifications were adopted in considering the viscosity of the blood, etc. (pages 408 and 409). In reality, resistance to flow probably varies with the pressure changes during the cycle and the whole system should be considered as one showing undulatory waves. When analysis takes this into account the complexity of the resulting mathematical deductions (Apéria[14]) places the treatment beyond the scope of most physiologists. The simplified schematic treatment allows certain mathematical deductions to be made, which, though not strictly true, help to clarify the situation. These are included here for convenience, though they are intended neither as precise statements of conditions in an undulatory system, nor as simplified statements to be memorized by students.

Elasticity, in physical terms, is the capacity of a system to regain its original shape or volume after distortion. The force tending to restore the original conditions is measured by Young's modulus of elasticity (the elasticity coefficient). It is the ratio of stress (pressure) to strain (per cent change in length or volume). In the vessels there are both transverse and longitudinal elasticity coefficients, and the two together give rise to the volume elasticity. A high coefficient implies the necessity for a high distending pressure. Age changes (hardening of vessels) cause an increase in the coefficient. This lack of distensibility, which commences to develop as soon as adult life is reached, or possibly even earlier, is partly offset by an increase in the volume of the arterial system, so that any given cardiac output forms a smaller proportion of the volume of the system. The change is particularly marked in the aorta itself as is indicated by the values for the ratio between the aorta and its branches that have already been given. Actually not only do the transverse diameters increase, but also the lengths of the vessels, and it is this increase in length which ultimately causes tortuosity.

The apparent tortuosity of vessels at autopsy fails to indicate the degree present in life, for the vessels lengthen considerably as their internal pressure is raised. Tortuosity also alters their distensibility, since a greater stretching force is developed when a wave is reflected round a bend. This effect probably intensifies the reservoir action of the aortic arch.

The elasticity of the system, which is of primary physiological importance is the volume elasticity coefficient, or the ratio of the pressure increase to the percentile increase in volume, $\left(\frac{dp}{\frac{dV}{V}}\right)$. The velocity of transmission of pressure by wave motion in an elastic system is also represented by the general equation:

$$\text{velocity} = \sqrt{\frac{\text{elasticity}}{\text{density}}}$$

In the circulation it depends on the volume elasticity coefficient and in this case the general equation may be reduced to the form:

$$v_p = \frac{3.57}{\sqrt{\%\text{ increase in volume per mm. Hg increase in pressure}}}$$

or, transposed:

$$\%\text{ increase in volume per mm. Hg increase in pressure} = \frac{12.7}{(v_p)^2},$$

as was pointed out by Bramwell and A. V. Hill.[48]

The conditions in the heart and blood vessels are also modified by the physical principles governing tension in a cylindrical tube. If σ_t represents the transverse stress per unit cross-sectional area of circular fibers in the wall, p the pressure, r the radius and a the thickness of the tube, then,

$$\sigma_t = \frac{pr}{a}$$

and from the relationships of volume to radius in a tube it may be deduced that

$$dV = \frac{2\ \pi\ r^3}{E_t a} \times dp$$

where E_t is the coefficient of transverse elasticity.

These two equations demonstrate how the development of transverse tension, stretching the muscle fibers of the heart or the walls of the large vessels, is not only a function of the internal pressure, but also of the original size of the vessel. They indicate the importance of the increase in size in the large vessels with age, since the extra volume accommodated with any small increase in pressure varies as the cube of the radius.

More exact estimates of these relations, which include consideration of Poisson's ratio (about 0.5 in the arteries) may be found in Frank's papers.[127] (It is uncertain how far his equations can be applied to the complex conditions of the living vessel.) Under *artificial* conditions even in life the velocity of wave transmission may be demonstrated to be related to the distending pressure[49, 162] but the elastic properties of contracted and relaxed arteries are very different[186, 223] and under different *physiological* conditions the pulse wave velocity cannot be predicted from the internal pressure.

Effective Peripheral Resistance.—The actual resistance cannot be usefully expressed in absolute terms in the present stage of our knowledge, since it varies with the number of small vessels and consequently with the size of the subject, as has already been explained (page 412). Until some quantitative study of this relationship has been made, rough approximations of the effective resistance must suffice. Some confusion exists in physiological literature owing to the use of the term "peripheral resistance" in different connections. Here it is used in reference to the viscous resistance to outflow from the large central vessels into the capillaries and veins; the small frictional loss of energy in the larger central vessels as well as the complexities introduced by wave motion and variations in resistance during the cycle are neglected. By some the term is used for the resistance which the heart has to overcome in expelling blood into the aorta, taking into consideration the effects of inertia. The two values are of similar magnitude but are not identical. The simplified considerations already mentioned in relation to experiments on blood viscosity will not be elaborated. It may be merely pointed out that expressions of the type under discussion, which relate blood flow to blood pressure, are only valid provided

blood flow is streamline in type. This is approximately the case under conditions of basal cardiac output. Eddies are generated at the aortic orifice as the blood flows through the constricted orifice into the dilated area beyond it (sinuses of Valsalva). These eddies serve to assist the functional efficiency of the valves. The eddies soon die out, for streamline motion in the dog's aorta has been demonstrated by Hess.[169] The extinction of the eddies depends on the presence of velocities below those critical for eddy generation or survival. These critical velocities vary inversely with the diameter of the vessel. Eddies should be extinguished in an aorta of 2 cm. diameter when the velocity falls below about 30 cm. a second. They should be generated in such a vessel (except for the complexities introduced by branching, etc.) only when the velocity exceeds 200 cm. a second. Eddies may obviously complicate the issue in the case of the rapid velocities that develop with high cardiac output in exercise or in marked aortic regurgitation even with the subject at rest.

Wave Reflection.—Much of the modification of the pulsatile waves generated in the vascular tree by the heart is dependent on reflected waves and on secondary waves developed as the result of vibrations in the vascular system. Some of the latter may be local, others involve the natural frequency of one or other arterial paths as a whole. Thus, in the central pulsations of the ascending aorta and innominate artery, small secondary waves are commonly seen on the ascending limb of the pulse (the Anfangschwingungen, or initial vibrations, of German writers). These were shown by Tigerstedt[296] to vary in frequency with the size of the animal and to depend probably on vibrations set up through stretch in the wall of the aortic arch. Other waves of longer duration probably depend on partial reflection of the main wave from points of branching, such as the bifurcation of the abdominal aorta.

When a wave travelling in an elastic system meets a closed obstruction at the end of the tube, it is reflected and at the point of reflection the wave can develop theoretically twice its previous height; actually various losses usually prevent its attaining more than two-thirds of this theoretical increase. The reflected wave then travels in the reverse direction and fuses with the remainder of the main wave; the total wave form depends on the time relations of the fusion of the two waves. Near the point of reflection the reflected wave fuses quickly with the incident wave, and creates a higher but narrow fused wave; on the other hand, in the aorta near the origin of the primary wave, the reflected wave arrives during the descending limb of this wave, on which, therefore, it creates a shoulder, and so generates a lower and broader fused wave. If a wave travelling in an elastic system meets an open tube offering no resistance, a positive wave is reflected as a negative wave, one theoretically capable of being equal in size to the original wave, but with the reverse sign. Obviously, reflection in the vascular system from the branching of large vessels into smaller, which have a greater total cross-sectional area, offers some compromise between reflection from closed and open tubes, and positive and negative reflections of both positive and negative waves must be considered possibilities.

Pulse Pressure and the Stroke Volume of the Heart.—The pulse pressure is determined by the magnitude of the stroke volume of the heart and by the volume and other physical constants (elasticity and length) of the arterial tree. Owing to the effects of wave reflection the pulse pressure varies in magnitude in any single pulse at different points in the system (see Figs. 160 and 161). Nor are these differences constant, for they are affected by local changes in the distensibility of the vessels, by changes in flow and pressure induced by increased cardiac output in exercise, by hyperthyroidism, aortic regurgitation, etc.[32, 173]

In spite of these complications many attempts have been made to calculate the stroke volume from the pulse pressure determined in the brachial artery by indirect methods. One of the simplest methods and one commonly used is to estimate the stroke volume as proportional to the pulse pressure divided by the mean pressure. Methods of such simplicity may give indications of changes in stroke volume of one individual, but allow only very inaccurate comparisons between individuals. A treatment has been advanced by Bazett and his co-workers which deals with the changes by means of algebraic equations. These take into consideration the probable volumes of different vessels, their distensibilities (as estimated from pulse wave velocity measurements) and involve a graphic integration of the pulse curve. Such simplified equations are entirely empirical and depend on standardization against respiratory methods. Standardized in this way they appear relatively reliable within a certain range. They depend admittedly on the false assumptions that the pulsatile flow can be considered without serious error as equivalent to a steady flow at the

same mean pressure. The equations can be considered valid only over the ranges in which they have been tested empirically. Other attempts have been made to calculate stroke volume from pulse pressure by considering the system in terms of equations representing undulatory motion. The difficulties to be overcome are discussed by Apéria.[14]

VASOMOTOR CONTROL OF THE ARTERIES AND ARTERIOLES

The existence of vasomotor nerves was demonstrated by Claude Bernard in 1852. He cut the cervical sympathetic nerve in the rabbit and noted the loss of vasomotor tone in the vessels of the ear on that side. He noted its replacement by constriction when the peripheral end of the cut nerve was stimulated. Later he also showed that active dilatation can be induced in the vessels of the submaxillary gland by stimulation of the chorda tympani. Vasomotor control is, therefore, commonly effected by two opposing systems. The central and efferent neurons which cause contraction of the circularly arranged smooth muscle of blood vessels are called *vasoconstrictor*. Those which produce relaxation of the vascular musculature are referred to as *vasodilator*. The term *vasomotor* is general and embraces both.

The main control of the peripheral resistance is obtained by variations in the degree of contraction of the muscular coats of the arterioles. These smooth muscles show slight contraction even when they are denervated. Under normal conditions this intrinsic muscular "tone" is augmented by tonically maintained impulses delivered by vasoconstrictor nerves of the sympathetic system. These repetitive impulses may be demonstrated electrically. When their frequency is reduced, the tonic contraction of the muscle is decreased. In addition, other nerves, the vasodilators, have the capacity to lower muscle tone by actively antagonizing the effects of the constrictors and by inhibiting the inherent tone of the vessels. A distinction is commonly drawn between the sympathetic vasoconstrictor nerves and parasympathetic vasodilators, but this is incorrect, for the functional differentiation does not follow this strictly anatomical nomenclature. The fibers affecting arteriolar tone belong to the following groups:

1. Vasoconstrictor fibers of sympathetic origin giving effects which resemble those produced by all but minimal doses of adrenalin. These fibers are adrenergic. The only well-established exception is in the supply of the coronary vessels where the sympathetic adrenergic fibers mediate vasodilatation. There the vasoconstrictors appear to belong to the parasympathetic division [see (2) below].

2. Vasoconstrictor fibers of parasympathetic origin. The vagal fibers to the coronary arteries are a proved example of this type of vasomotor innervation. Reactions similar in type to those evoked by these fibers are produced by acetylcholine, and these nerves are believed to exert their action by the liberation of some choline compound. They are therefore known as "cholinergic."

3. Vasodilator fibers which are branches of a sensory nerve. These fibers end in the muscular wall of the vessels and when stimulated produce vasodilatation. They also are "cholinergic." They are certainly concerned in axon reflexes (see page 177), and they can produce vasodilatation (as in inflammatory reactions) as part of a peripheral mechanism which does not require the intervention of the central nervous system.

3a. Vasodilator fibers which emerge from the spinal cord via the posterior roots and which from their unexpected origin are known as "antidromic"

fibers. These are cholinergic and they may be identical with Group 3. The chief differentiation would then depend on the participation of this group in true reflexes mediated through the intervention of the central nervous system. Good evidence exists that impulses may leave the cord via the posterior roots (see page 95), but the identification of these impulses with vasomotor reactions is less certain.

4. Parasympathetic vasodilator nerves. These may be subdivided on the basis of the cranial and sacral portions of this division of the autonomic system. The former are found in cranial nerves III, VII, IX, and X, and include vasodilators to the salivary glands, tongue and larynx. There is no evidence that the vagus carries vasodilator fibers to the abdominal viscera. These cranial autonomics may in reality be cranial members of Group 3. At any rate, the chorda tympani receives many of its fibers from unipolar cells comparable to those of the posterior root ganglia.[298] Nerves such as the chorda tympani are distributed not only to gland cells but also to blood vessels (including the capillaries) (Sihler[283]). These fibers, like those of Group 3, are cholinergic in type. While the secretory functions, such as those on the salivary glands, are readily antagonized by atropine (as is the action of the vagus on the heart), the vasodilator effects, both of this group and of Group 3, are only antagonized by very large doses of this drug.

The sacral autonomic fibers include the nervi erigentes which are concerned in the special vasodilatation of erection. They leave the cord by the anterior roots and are probably "cholinergic."

5. Vasodilator nerves which have, anatomically, a sympathetic distribution but which exert effects that appear to be cholinergic. They may be called "cholinergic" sympathetic vasodilators.

6. Vasodilators with an anatomical distribution which is sympathetic and giving reactions similar to those produced by adrenalin. To this group belong the dilators of the coronaries. These may be classed as "adrenergic" sympathetic vasodilators.

The arterioles are profoundly affected by products of metabolism, by secretions of certain glands such as the adrenals, and by temperature changes. The tone of the muscular coat is, therefore, the resultant of a large number of regulating influences and even the effects of nerve stimulation appear to be the results of the local liberation of chemical substances.

It is important to bear in mind that under normal conditions the effects of the elaboration of a chemical mediator are limited to the immediate site of origin. Acetylcholine is destroyed at once on entering the blood and to detect the presence of sympathin in the blood requires the use of an effector sensitized by denervation.

Vasoconstrictor Control.—Impulses pass from centers in the medulla down the anterolateral columns to cells in the lateral horns. There they excite preganglionic neurons running to sympathetic ganglia and thence they are transmitted by postganglionic nonmedullated fibers to the vessels. The latter fibers travel with the peripheral nerves, and leave at intervals to join the periarterial nerve plexus. In this they course only a short distance before terminating. It is for this reason that the operation of periarterial sympathectomy is ineffective in producing vasodilatation distally or relief of arteriolar spasm.

Impulses of the type shown in Fig. 168 may be recorded in such nerves. If the peripheral nerves be cut so as to divide both vasoconstrictor and dilator fibers an immediate dilatation results. From this it follows that the tonically active fibers must be mainly vasoconstrictor in function. If a series of tetanic shocks be applied to the sympathetic nerves an intense vasoconstriction is produced in the region innervated. The effect may be demonstrated by a decreased rate of flow through a vessel perfused at a constant pressure. A record obtained in this way in a frog is shown in Fig. 169. The vasoconstrictor response lasts for some time after cessation of the stimulus and then slowly fades. The rate of its disappearance may be greatly accelerated by stimulation of the distal end of a cut posterior root, which has an antagonistic vasodilator action. A similar inhibition of the constriction is produced if acetylcholine is added to the perfusing fluid. When the posterior root is inactive, even a single shock applied to the sympathetic nerve can produce constriction, but repetitive stimulation, even at a low frequency (Fig. 170) is more effective and builds up a summated response. A weak contraction may be inhibited by posterior root stimulation,

Fig. 168.—Vasoconstrictor impulses in a sympathetic nerve. Time marker indicates 0.2 second intervals. (From Bronk: Harvey Lecture on the Nervous Mechanism of Cardio-Vascular Control, Baltimore, 1934, The Williams and Wilkins Company.)

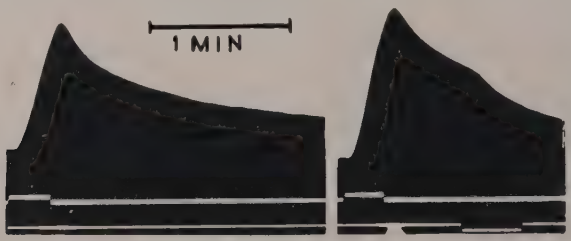


Fig. 169.—Constriction of vessels in frog produced by stimulation of sympathetic during period indicated by the upper signal. In the record at the right the dorsal roots were stimulated during relaxation (indicated by the lower signal). (From Bozler: Am. J. Physiol. **117**: 457, 1936.)

even during the maintenance of sympathetic excitation. On the other hand, if the rate of stimulation of the sympathetic is increased and is made maximal, it can cause constriction in spite of a simultaneous maximal stimulation of the posterior root. The effect produced is then a balanced effect of opposing forces of varying magnitude, comparable to the antagonistic effects of the vagus and accelerators on the heart.

The reflex production of vasoconstriction may be accompanied not only by an increase in the impulses of the vasoconstrictor nerves but also by impulses in nerves of the same type that go to the adrenal glands and produce a secretion of adrenalin. This will be discussed later in connection with the reflex control (page 474). The motor effect may be studied by electrical stimulation of the peripheral end of a cut splanchnic nerve, which carries vasoconstrictor nerves to the mesenteric vessels as well as fibers which evoke adrenalin secretion (Fig. 171).

If the experiment be made in a decapitate animal under artificial respiration, any modification of the response by secondary reflexes initiated by the rise in pressure is avoided. The pressure is at first at a low level due to the absence of vasomotor tone through the removal of the medullary centers. On stimulation the blood pressure rises through increased peripheral resistance caused by vasoconstriction. The heart, contracting against this greater resistance, has its stroke volume at first slightly reduced, so that the pulse pressure is also lessened. The residual blood left in the ventricle as the result of its ineffective emptying increases its diastolic volume, improves its contraction and helps it to meet the load. This compensation is aided later by a second change due to adrenalin secretion. The pulse rate, which was originally unchanged, is increased, the pulse pressure becomes greater and the whole pressure level shows a secondary rise. This secondary change is dependent mainly on an increased cardiac output, possibly slightly on an increased peripheral resistance through the additional effect of adrenalin. The delay in the secondary changes is dependent on the time required for

Fig. 170.—Response of blood vessels to a series of sympathetic and dorsal root volleys. One stimulus applied to sympathetic about every 1.5 seconds (lower signal). The upper signal indicates the beginning of dorsal root stimulation (20 per second). (From Bozler: Am. J. Physiol. **117**: 457, 1936.)

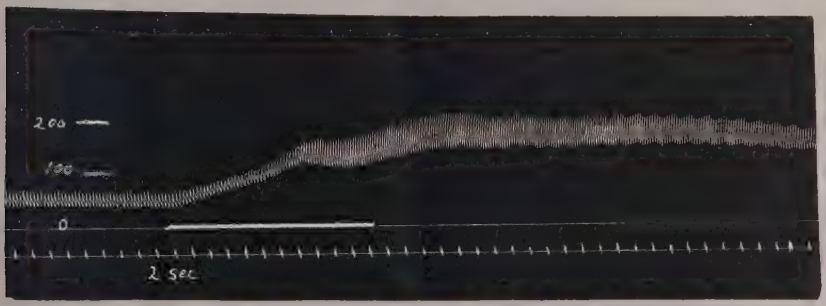


Fig. 171.—Record of carotid pressure in a decapitate cat on stimulation of the peripheral end of the right splanchnic nerve with the adrenals intact. The record was obtained by a membrane manometer and the signal below the record indicates the atmospheric pressure level and the time of stimulation. Standardization of the manometer in mm. Hg is shown on the left. Note the initial increase in pressure without increase in pulse rate and with only minor changes in pulse pressure followed by a secondary rise accompanied by a marked increase both in pulse rate and in pulse pressure.

the blood leaving the adrenal gland to reach the coronary circulation. That the changes are in fact due to adrenalin secretion may be shown by ligating the adrenal veins after which the secondary rise in pressure and increase in pulse pressure and pulse rate do not occur. The adrenalin output sometimes induces ventricular extrasystoles and causes irregularities in the pulse. A slight fall in pressure just preceding the secondary rise (see Fig. 171) is common. It is contemporaneous with the onset of an increased pulse rate and probably depends on coronary dilatation induced by adrenalin.

If an anesthetized intact animal be employed for this experiment instead of a decapitate preparation (which has no vasomotor center) the responses described are modified by reflex

changes initiated by the pressure rise. Consequently the curves obtained are complex. Under certain anesthetics (e.g., choralose) hyperexcitability of cardiac muscle may also be prominent and cause numerous ventricular extrasystoles. These sometimes occur in the early stage of increased cardiac work before the output of adrenalin, sometimes in the later stages of a prolonged pressure rise. They complicate still further the blood pressure picture. They may develop even where the vagi have been cut.

Hypersensitivity to chemical stimuli after denervation and degeneration of the nerves is a striking phenomenon in the structures innervated by the sympathetic. Hypersensitivity to small amounts of adrenalin may produce exaggerated responses closely resembling the nervous response. According to White,[309] this hypersensitivity does not develop if the preganglionic connections are divided, and the postganglionic nerves are left intact. The development of an increased sensitivity to adrenalin (and sympathin) should be considered in the treatment of vascular spasm by sympathetic denervation.

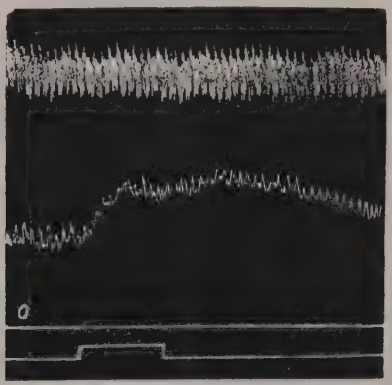


Fig. 172.—Blood pressure (upper record) and volume of the hind leg (lower record). At the signal, stimulation of the peripheral end of the posterior root of the first sacral nerve. The entire lumbar cord had been removed previously. The anterior roots and the portions of the posterior roots lying central to their ganglia had degenerated. The effect (increase in leg volume) must therefore depend on a peripheral action of posterior root stimulation. (From Bayliss: J. Physiol. 26: 173, 1900-1901.)

Vasodilator Control.—The diminution of vasoconstrictor effects by posterior root stimulation has already been considered (see also Fig. 172). Presumably these effects are produced by fibers concerned in the axon reflexes.

Vasodilatation of the axon type is supposedly involved in local inflammatory reactions. Such reactions may occur in the absence of sympathetic fibers and when the sensory nerves are no longer in connection with the central nervous system provided they have not degenerated.[53] These nerves probably release some chemical substance. Lewis and Marvin[219] obtained vasodilatation in the fore-limb of a sympathectomized cat on stimulation of the distal ends of the appropriate posterior roots. This dilatation lasted only a short time when the circulation was free. If, however, the nerves were stimulated while the circulation was obstructed by a Riva Rocci cuff, they produced their effect minutes later on release of the obstruction.

Vasodilators of the antidromic type are more difficult to demonstrate with certainty, but some of the reflex responses to be described later appear to indicate

their existence. With them may be classed the vasodilators of the parasympathetic type. The nervi erigentes, however, cannot be so classified.

Sympathetic fibers mediating vasodilatation may be cholinergic or adrenergic. It was shown by Dale that ergotoxin paralyzes the vasoconstrictor action of the sympathetic. After administration of this drug stimulation of the splanchnic produces dilatation instead of constriction in the vessels of the gut and stimulation of the abdominal sympathetic chain produces dilatation in the vessels of the hind limbs. Burn[56] found that in the dog stimulation of the abdominal sympathetic without ergotoxine produces dilatation in the hind limb, and that the fibers involved are "cholinergic" in that their effects are intensified by eserine and paralyzed by atropine. Nerve fibers, therefore, which must be classed as sympathetic on anatomical grounds may be cholinergic. The sympathetic also innervates the coronaries and here its main effect appears to be vasodilatation. It is probable that some sympathetic vasodilators produce their effects by the local liberation of sympathin I.

Chemical Substances and Vasomotor Tone.—On stimulation of the motor nerves to skeletal muscles, some vasoconstriction and decrease in blood flow may result if the stimulating current is at low frequency. It is probably due to sympathetic stimulation. This effect occurs more readily if the actual contraction is prevented by curare. On the other hand, if the muscle is allowed to contract, a brief period of constriction may be followed by a prolonged period of vasodilatation. The time relations of the latter response and its suppression by curare indicate that it is due to the vasodilator action of metabolites. Among these are carbon dioxide and acids such as lactic. Although some writers have thought that the threshold necessary for such local action of acid metabolites is not reached under normal conditions, Fleisch[123] has shown that the hind limb of an animal perfused with blood from a heart-lung preparation shows vasodilatation (as evidenced by greater flow at the same arterial pressure), if the lungs of the preparation are ventilated either by air containing a small amount of CO_2 or by air deficient in O_2. Such reactions must be of chemical origin. Production of histamine during the activity of both skeletal and heart muscle has been described.[11, 12] It may be intimately concerned with vascular changes. Histamine causes a pronounced dilatation of capillaries. In some animals it produces relaxation of the smaller arteries. The larger arteries are, however, in many species constricted by histamine.[57] It is uncertain how far it can account for general vasodilatation. Acetylcholine dilates arteries and, as mentioned in Chapter VIII, it may be the mediator of motor impulses to skeletal muscle. Adenylic acid and products of nuclear metabolism are said to occur in the venous blood leaving active muscles. They are very powerful vasodilators.[98] Adrenalin in weak doses causes vasodilatation, in stronger concentrations vasoconstriction. In moderate doses it may cause constriction of the splanchnic and skin vessels and vasodilatation in the muscles. The threshold value that produces vasoconstriction instead of vasodilatation appears to vary not only with different tissues but also in the same tissue with variations in the pH of the blood. The threshold is lower the more alkaline the blood.[53] This fact may account for the greater readiness with which dilatation is obtained in muscular areas where activity is accompanied by development of considerable acidity. Pitressin may also cause vasoconstriction.

Changes in temperature also produce effects on the vessels. To some extent these are direct effects, to some extent reflex adjustments. Even a completely denervated area, in which the nerves have degenerated, shows changes in response to altered temperature. Cold causes constriction with slowing of the flow of blood, warmth gives dilatation and increased rate of flow. Similar changes are seen in an innervated area but the mechanisms involved are much more complex. Warmth can cause vasodilatation of arterioles, capillaries, veins, and probably also of arterio-venous anastomoses and the dilatation may involve neighboring areas not themselves exposed to the temperature change. If the area exposed to warmth or cold is sufficient to necessitate considerable adjustments in order to maintain body temperature within the normal range, the circulation throughout the whole body may be modified. If local changes in temperature are sufficient to threaten damage to the tissues and to cause pain, axon reflexes may be involved. These may result in arteriolar dilatation whether the excessive change be heat or cold. Changes in temperature in the peripheral parts of the body induced by thermal stimuli, may amount to as much as 10°-20° C. or more. Such changes result in considerable alterations in

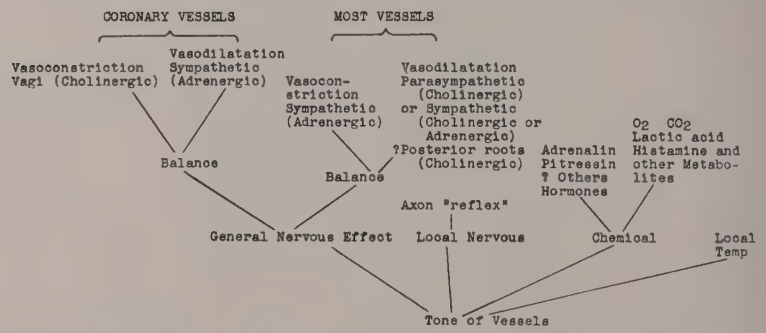


Fig. 173.—Outline of the factors which control the tone of the blood vessels.

the acidity of the blood[36] as well as in the metabolism of the tissues. It is therefore extremely difficult to decide in the intact animal the extent to which changes are dependent on the direct effects of the altered temperature, on secondary chemical effects, or on reflex reactions either of the axon or the central type.

Vasomotor Changes in the Large Arteries.—Little is known of such changes, but it is unlikely that the muscular coat is without function. Painting the aorta with cocaine is found to modify considerably the pulse in the femoral artery.[185] Bazett and his collaborators[37] found that the velocity of the pulse wave in the large arteries is increased under conditions (digestion of a meal and exposure to warmth) in which small arteries are dilated; the changes in the larger and smaller vessels appear to be consistently reciprocal. This would be explicable if such adjustments serve to regulate the total vascular capacity. It is noticeable that the reactions of large arteries to drugs such as histamine may be exactly the reverse of those of smaller arteries. Direct evidence has recently been advanced that the larger vessels can show marked contractions.[280] One may tentatively assume a constriction of large arteries as an accompaniment of diffuse peripheral dilatation.

Demonstration of Effects of Vasomotor Nerves.—If the arterial bed affected is large, vasomotor changes may be demonstrated by the alterations in general arterial blood pressure induced by stimulation. Thus stimulation of the peripheral end of the splanchnic normally produces a pronounced rise in mean arterial pressure. The presence of vasoconstriction may be also demonstrated by the use of a plethysmograph or volume recorder, similar in principle to the cardiometer already described. The volume changes may be recorded, through the displacement of oil or air, by a light piston recorder, Brodie bellows, or light tambour. The change in volume of the hind limb that results from stimulation of the peripheral end of a posterior nerve root is shown in Fig. 172.

The presence of vasomotor changes may also be demonstrated by alterations in the arterial inflow or venous outflow (the method utilized in obtaining the records shown in Figs. 169 and 170), provided that the changes observed are not explicable as the simple physical results of changes in blood pressure. Variations in temperature or in thermal conductance produced by alterations in flow constitute another useful indication.[58]

Summary of Vasomotor Changes.—Many of the effects induced in vessels by nervous factors probably represent algebraic summations of the effects developed by vasoconstrictor and vasodilator nerves. (Many vessels, however, lack a vasodilator innervation.) As will be seen later these antagonistic nerve supplies tend to be activated in a reciprocal manner, so that vasoconstrictor impulses, which normally have a high tonic outflow, are decreased as vasodilator impulses are increased and vice versa. Also any extensive dilatation in one area tends to be accompanied by constriction in another. The general relationships of the changes are shown diagrammatically in Fig. 173. At this stage the reader may obtain a clearer idea of the diverse controls of the circulatory system by fitting together Figs. 146, 152, and 173. If Fig. 152 be placed below, Fig. 146 above it to the left, and Fig. 173 above it to the right, a general picture of the control mechanisms of the arterial system may be obtained.

THE CIRCULATION IN THE CAPILLARIES

Capillary Contractility

The circulation in the capillaries is remarkable for the great broadening of the stream bed and its division into numerous small vessels. As a result of this the rate of flow is slowed and the surface to which the blood is exposed is enormously increased. The figures given in Table XII illustrate these points. It has been calculated by Krogh[205] that the total surface of the capillaries in a man would be of the order of 6,300 square meters. The total number of capillaries is very large. If they were all dilated at one time the blood volume would have to be much increased to fill adequately the vascular system. Normally at any one time only a portion of the capillaries are functioning. It is only when a tissue is in full activity that all of its capillaries are brought into action. According to Krogh the number of open capillaries in active muscle may be one hundred times as great as that in resting muscle. According to Martin, Woolley and Miller[231] the increase is fourfold while Sjöstrand[285] claims that only two and one-half times as many capillaries are open in active as in resting muscle. In any case the number can be greatly increased. This variation in number is dependent on an independent contractility of the capillaries which is attained, according to Krogh and Vimtrup, through the action of special cells with netlike processes which surround the capillaries. These are called Rouget cells after their original discoverer.

The Clarks,[71] who have made extensive studies of the capillaries in the rabbit through a transparent window set aseptically in the ear, have not observed spontaneous contractions

in the capillaries and consider that the Rouget cells are wandering connective tissue cells. Florey and Carleton[125] observed contractility in mesenteric capillaries but found no evidence of its dependence on Rouget cells. Kahn and Pollak[190] describe contractility of two kinds, one due to constriction by cells lying outside the capillary, the other due to swelling of the nuclei of the endothelial cells. Since there is abundant evidence of contractility of capillaries in some areas, Krogh's viewpoint is the one most likely to be established ultimately. When the tissue is at rest the contraction of capillaries is intermittent; there is a rotation of active vessels. Such intermittency has been described also in the glomerular capillaries of the kidney.

Lewis[216] considers that in the skin there is normally no intermittence but certainly all the capillaries are not open. In unpublished observations by Dr. Ella Roberts only 25 capillaries per field could normally be seen at the root of a nail but after histamine injection in the neighborhood the number was increased to 70 and this number was never exceeded. On sudden return from a colder climate to Philadelphia in hot weather the normal number increased gradually and after two or three days all the capillaries were open and no further increase could be obtained even with histamine.

The capacity of capillaries to constrict forcibly was pointed out by Cotton, Slade and Lewis[76] who experimented on the constriction of capillaries and venules in response to adrenalin. They found that this constriction could not be overcome until the venous pressure was raised to 80 mm. by partial inflation of a Riva-Rocci cuff round the arm, and that it could develop against a venous and capillary pressure raised to 30 to 40 mm.

Capillary Pressure

Measurement of Capillary Pressure.—The capillaries may be readily observed under the microscope in the web of the frog's foot, in the frog or mammalian mesentery, in the rabbit's ear (by means of Clark's special chambers[73]) and in man in places where the skin is thin (root of the nail; prepuce). Human skin can be made semitransparent by means of cedar-wood oil. Capillary pressure, however, can be accurately measured only by the introduction under a microscope of a fine capillary pipette. The intracapillary pressure is then found from the pressures necessary to cause transference of fluid in either direction. This direct method was employed originally by Landis.[210] Capillary pressure may be estimated very roughly by determining the pressure, which, when applied to the skin, causes blanching. This method is similar to that utilized for the indirect measurement of venous pressure. As the color of the skin depends on the blood content of various minute vessels (venules, capillaries, etc.) which have different internal pressures, no sharp end point is attained. If, however, a small glass capsule with a cover of goldbeaters skin is used for the compression, the capillaries may be watched under the microscope.[182] In this way better estimates are obtained but the gradient of pressure in the capillaries prevents the attainment of accurate values.

The Level of Capillary Pressure.—The normal pressure in the capillaries has been illustrated in Table XII (page 338). The figures suggest a value some 56 mm. below the mean pressure in the mesenteric artery, or one of about 24 mm. Hg. The direct observations of Landis[210] gave similar values for mammals (Fig. 101, page 340). The average capillary pressure is not determined by the degree of capillary contractility, but rather by the balance between filtration pressure within the capillaries (which tends to force fluid out into the tissues) and the osmotic pressure of the plasma proteins (which tends to retain fluid or to cause it to pass from the tissues into the capillaries). For this reason the *average* capillary pressure tends to remain constant and to be relatively independent of the circulatory conditions, provided that a normal capillary permeability is retained. The capillary pressure may be considered as the reference point of the circulation. The arterial pressure is raised above, the venous pressure lowered below it (see page 340).

In an *individual* capillary the pressure may deviate considerably from the average value. It is dependent (1) on the arteriolar resistance which accounts

for a loss of pressure head between the large arteries and the capillary, and (2) on the pressure in the vein. The degree of constriction of the capillary itself has little effect except in determining the pressure gradient along the capillary with the flow obtaining at the moment. The pressure gradient in a capillary is dependent on the rate of flow (as determined by the conditions in the arterioles and veins), and on the size of its lumen, whether this be affected passively, or as the result of its own contractility. Vasodilatation of the arterioles not only causes a more rapid inflow to the capillary but raises the pressure at its arterial end, for the arteriolar relaxation decreases the change in pressure head between arterioles and capillaries. The increased flow tends, on the other hand, to steepen the pressure gradient along the capillaries and veins. Venous congestion with rise in venous pressure also raises the capillary pressure, but it decreases flow and the pressure gradients along the vessels. If this rise in venous pressure is adequate to enlarge the small vessels, the resistance they offer to flow may be decreased. Thus in some instances mild congestion may give rise to an increased flow, but whether the flow be decreased or increased, the pressure gradients are reduced. The condition of increased flow with venous congestion has been shown to occur when the hand is allowed to hang down (Goldschmidt and Light[142]).

The low pressures found in capillaries, veins, cerebrospinal fluid, etc., are normally measured in centimeters of water, and are commonly expressed in these units. Such values are difficult to compare with others given in millimeters of Hg. For this reason all the values are here stated in millimeters of Hg.

The general effect of local vasodilatation on capillary pressures and gradients is indicated in Fig. 174. This shows that arteriolar dilatation produced by heat raises the pressure at both the arteriolar and the venous ends. Consequently the whole pressure level is raised, with the result that filtration of fluid must be increased. The gradient of pressure in the capillaries is reduced in spite of a more rapid flow. This reduction must be the result of a lowering of the resistance offered by the capillaries, either because of an increase in the lumina of individual capillaries or through the opening up of additional paths or by both these means.

Osmotic Balance in the Capillaries.—The essential character of this balance has already been described (pages 335 to 337). The colloid osmotic pressure exerted by the plasma proteins is not only dependent on their total concentration but also on the relative amounts of the different plasma proteins.

Osmotic Pressure of the Plasma Proteins.—The effective osmotic pressure of the proteins depends, according to Govaerts, very largely on the albumin molecules, for these are the smaller and more numerous, and exercise, therefore, the greater osmotic pressure. For the same reason they escape more readily when the capillary walls are damaged. Thus a moderate lowering of the total plasma proteins may cause a considerable fall in osmotic pressure. The normal level of plasma proteins in man (disregarding minor sex differences) is, according to Peters and van Slyke,[248] 7 Gm. per 100 ml. of plasma. The albumin content is 4.40, the globulin content 2.63 (albumin/globulin ratio of 1.67). The osmotic pressure of the albumin is said to be 5.5 mm. of Hg per Gm., or a total of 24.2 mm.; that of globulin 1.4 mm. per Gm. or 3.7 mm. The total colloid osmotic pressure would on this estimation be 27.9 mm. The critical level at which lowering of osmotic pressure tends to give edema (through incapacity of the organism to lower capillary pressure proportionately) is (according to van Slyke) in renal cases a total protein content of 5.5 per cent. This may be associated with an albumin concentration of only 2.5 per cent (i.e., the albumin/globulin ratio may be reduced to 0.84). Under such conditions the colloid osmotic pressure would be (13.7 + 4.2)

or 17.9 mm. The difficulty of maintaining a capillary pressure low enough to create a balance at such a level, while also maintaining an adequate pressure gradient for the return of blood along the veins, is obvious. Normally there is a pressure gradient between the mid-region of the capillary and the venules of some 15 mm. and any reduction in viscosity would not be adequate to reduce this fall to any extent. The residual gradient for flow in the larger veins would be very low.

The protein concentration of tissue fluid appears to be normally quite low. Consequently, there is an *effective osmotic pressure* of 25 mm. Hg or more between the plasma and this fluid. The tendency to absorb fluid into the capillary is off-set by the hydrostatic pressure within the vessel which tends to drive fluid into the tissues; this is the *filtration pressure.* The hydrostatic pressure of the

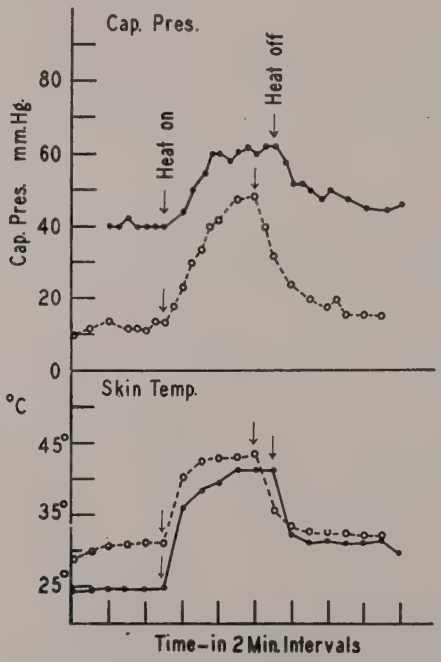


Fig. 174.—The effect of increase in temperature on the pressures in skin capillaries. The heavy line represents pressures in the arteriolar end; the dotted line, pressure in the venous end of a capillary. Two separate experiments are indicated, and the skin temperatures observed in each are shown in the lower graph. (From data reported by Landis: Heart, 15: 209, 1930.)

fluid in tissue spaces is normally quite low though somewhat in excess of atmospheric pressure. Under certain conditions the tissue fluid pressure may be raised and filtration is then hindered since the movement of fluid must depend on the difference in pressure between the capillaries and tissue fluids. The *effective filtration pressure* is therefore determined by the difference in these hydrostatic pressures and fluid balance by the relation of this difference to that in colloid osmotic pressures. When the difference in hydrostatic pressures exceeds the difference in osmotic pressures, fluid passes into the tissues; when it is less, fluid is absorbed into the blood stream. Fluid normally passes into the

tissues from the plasma at the arteriolar end of a capillary and from the tissues to the blood at the venous end. In this way a constant movement of fluid is maintained. The rate of fluid transfer observed by Landis in the mesenteric vessels of the frog is indicated in Fig. 175. It may be noted that the actual rate of transfer was that which would be anticipated from the observed pressures, if tissue fluid pressure be considered to be nearly at the atmospheric level.

When the capillary wall is damaged proteins are no longer adequately retained. The effective osmotic pressure within the vessels is then reduced and not only the rate of fluid transfer, but also the pressure level of the equilibrium at which no transfer of fluid occurs is altered. This is also indicated in Fig. 175. When the capillary walls are exposed to oxygen lack, even in a frog for as short a time as three minutes, they are damaged and become permeable to protein. If the period of anoxia has not been too long a normal permeability is rapidly regained when the oxygen supply is renewed. Protein lost to the tissues

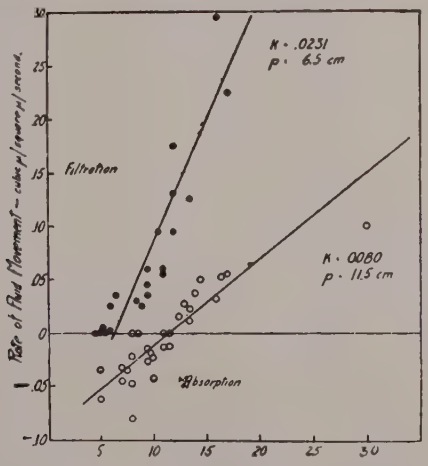


Fig. 175.—Chart showing the rate of filtration in frog's mesenteric capillary one minute (dots) and fifteen minutes (circles) after a three-minute interruption of blood flow. The effect of oxygen-lack is shown by the greater steepness of the upper curve. Ordinates indicate the rate of fluid movement in cubic micra per square micron of capillary wall per second; abscissae, the capillary pressure in centimeters of water. K is the filtration constant representing filtration rate; p, the apparent effective osmotic pressure of the plasma proteins or the pressures at which no fluid transfer occurred. (From Landis: Am. J. Physiol. 83: 528, 1928.)

cannot then return to the capillaries and the effective osmotic pressure would be reduced through an increase in the colloid osmotic pressure of the tissue fluids. As will be seen later this effect is probably prevented because the escaped protein can pass readily into the lymphatic system where by absorption of fluid it may be concentrated and ultimately returned to the blood stream. The importance of lymphatics under conditions of temporary or continued damage to the capillaries is obvious. The relation of capillary filtration to lymph formation is fully discussed by Landis.[210]

Evidence indicates that the permeability of capillaries is greater when they are perfused with solutions containing no particulate matter. The larger particles, such as red blood corpuscles, can, by adhering to the walls, block incipient leaks (Zweifach[329]).

Arteriovenous Anastomoses.—In certain areas direct connections exist between the arterioles and veins, so that blood may be shifted from one to the other without going through a capillary system. The connecting vessels have a strongly developed muscular coat, and are under nervous control. Detailed descriptions of such anastomoses in the superficial vessels of the skin are given by Grant[145, 146] and by the Clarks.[72] In areas such as the skin these vessels are often closed. They open when the individual is exposed to heat, and then probably assist the loss of heat by facilitating a rapid flow of blood through the superficial veins. They may also open on exposure to extreme cold. In this case the response probably helps to prevent too great a cooling of a local area. Such anastomoses have also been found in the kidney and intestine. Possibly they exist in other tissues. Their functions in internal organs are unknown, but in any area their opening would create considerable modifications in the pressure gradients in the vessels.

Control of the Capillaries

A direct sympathetic nerve supply to the capillaries has been described. Capillaries are also influenced by posterior root fibers, either directly or through the release of some chemical mediator in their neighborhood. Doi[93] has claimed that stimulation of the posterior roots produces capillary dilatation in the frog even after acetylcholine has previously maximally dilated the arterioles. Under the conditions capillary dilatation could not, therefore, be passive, and secondary to increase in internal pressure. During activity dilatation of the capillaries accompanies dilatation of the arteries and veins. This effect may be produced by metabolites. A metabolite which may be effective in this respect is some histamine-like substance, for histamine dilates capillaries in mammals (though not in frogs). Dilatation of capillaries is indicated by a considerable increase in the volume of a perfused limb with little decrease in peripheral resistance,[83] since the resistance offered by the capillaries themselves is normally only about ⅛ of the total. Histamine is liberated during the activity of skeletal and heart muscle.[11, 12] Adrenalin in the smallest concentrations appears to assist in the maintenance of capillary tone; in larger concentrations it causes dilatation, and in still larger doses contraction. Pitressin, the vasoconstrictor principle found in postpituitary extracts, appears to cause long-maintained contraction of capillaries. It is uncertain whether adrenalin and pitressin are responsible for the maintenance of normal capillary tone. On the other hand, there is good evidence that carbon dioxide and some metabolite formed during oxygen lack cause capillary dilatation. Some histamine-like substance may be involved in the production of the dilatation of inflammation. Temperature changes are also effective; warmth produces dilatation, moderate cold constriction and excessive cold a dilatation which is probably paralytic.

A great deal of information has been derived from studies of inflammatory and similar reactions in the skin. Because of their clinical interest these must be described in some detail. The similarity between these reactions and those to histamine and inflammation is very striking in certain respects but in others marked contrasts are found.

Vascular Responses of the Skin

The color of the skin depends on the amount of blood contained in superficial capillaries and venules; the temperature of the skin varies with the volume

of blood flow. The flow is not directly related to the number or size of the vessels. A warm pale skin indicates a relatively rapid cutaneous circulation with constriction of the capillaries and venules. A cold pale skin indicates that the arterioles are also constricted. The red cold skin produced by exposure to extreme cold is associated with arteriolar constriction and a very slow blood flow through dilated capillaries and venules.

If under normal conditions a blunt point be drawn lightly over the skin, there slowly develops a white line, exactly limited to the area stimulated. The latent period of its development is some seconds; it lasts a few minutes and then gradually fades.[76] That it is capillary in origin is indicated by microscopic examination and by the fact that it may develop when the circulation has been occluded, a condition in which arteriolar constriction could not modify the filling of the capillaries. It is not dependent on nerves, for it may be obtained in denervated areas. It must, therefore, depend on a direct response of the capillaries to irritation or to some substance which is liberated as a result of the mechanical stimulus.

A somewhat different response occurs when the stroke across the skin is made with some force. This is especially well seen in sensitive skins. It is the so-called "triple response" which has a latency of about twenty seconds and requires about three minutes to reach its maximum. It may be divided into three distinct parts or aspects. (1) Along the course of the stroke there is a *red line* due to capillary dilatation. On either side of this a pale area of capillary constriction may often be seen. Both probably depend on direct reactions of the capillaries to injury or to chemical substances (possibly histamine or histamine-like substances) engendered by the injury. (2) There next develops, in an area (possibly several centimeters in width) surrounding the first response, a *flare* which is produced by arteriolar dilatation. Here the rate of blood flow and the skin temperature are increased, but the capillaries are also dilated. This reaction depends on the presence of nerves, but their connection with the central nervous system is not essential. It is probably an axon reflex initiated by some irritative chemical change (perhaps formation of histamine) at the point of injury. (3) A *wheal* may be formed along the initial line of the stroke or scratch. This results from extrusion of fluid into the skin, and it is probably due to the action of a histamine-like substance on capillary permeability. A similar triple response may be obtained by pricking a minute quantity of dilute (1 part in 1000) histamine into the skin. A definite central wheal with local capillary dilatation surrounded by a flare of irregularly circular shape is induced. If the stimulus, either in the form of a stroke or injection of histamine, is applied while the circulation is occluded by arterial compression, the flare does not fade for some time after the blood flow has been restored. The time required for fading is in this case the same as when the flare is set up while the blood is circulating. The disappearance of the reaction is apparently due to the removal of the exciting chemical substance by the blood. According to Lewis[216] the mechanical stimulus of the stroke causes the liberation of some substance similar to histamine. This he calls the H-substance; it is probably not histamine itself.

When the circulation of a limb is occluded by rapidly distending a Riva-Rocci armlet to a pressure above that in the arteries, the limb becomes cyanotic if the occlusion is maintained. The cyanosis develops more rapidly the higher

the temperature of the limb. After release of the occlusion a general dilatation of the skin vessels is seen. The skin assumes a bright red color and the change is sharply limited to the area previously deprived of blood. There is an increase not only in the total blood content of the tissues (hyperemia) but also in the velocity of blood flow. This response as a whole is known as *reactive hyperemia.* At any given temperature the degree of hyperemia, measured in terms of the rate of blood flow, is determined by the duration of the occlusion; it is greater at higher temperatures. Freeman[129] has shown that the absolute volume of the increased blood flow is related to the extent of the blood debt which provoked it. The phenomenon is most reasonably explained as the result of the accumulation of some metabolite. Lewis attributes it to the action of H-substance accumulated during the stasis, but there is evidence that this is not the agent concerned.

It has been shown by Goldschmidt and McGlone[143] that oxygen may penetrate a short distance into the skin. Thus if a limb be occluded in an atmosphere of pure oxygen, no cyanosis develops in areas where the skin is relatively thin. If now the occlusion be released, no reactive hyperemia occurs in the areas free from cyanosis. The reaction appears, therefore, to depend on oxygen lack. Owing to the cyanosis no definite flare can be made out when histamine is injected into the skin of an occluded arm in air. On the basis of this and other facts Lewis has assumed that the flare is entirely arteriolar in origin. However, when the occluded arm is placed in oxygen the cyanosis disappears and a flare becomes evident at the site of a histamine puncture, though no wheal develops. On release of the occlusion the histamine wheal appears, the flare stands out more prominently, but reactive hyperemia does not occur. These facts indicate (1) that the flare must be due, at least in part, to capillary dilatation, (2) that the flare can develop in the absence of blood flow despite the presence of oxygen, (3) that the flare and the wheal on the one hand and reactive hyperemia on the other have different causes. Lactic acid or some other acid product of anaerobic reactions in cells is a probable cause of the reactive hyperemia, for the factors which modify the degree of hyperemia modify similarly the acidity developed in the tissues.

The variations in capillary tone which result from moderate changes in skin temperature have also been ascribed by Lewis to variations in the production of H-substance. They are as likely to depend, however, on alterations in oxygen tension or acid-base equilibrium which attend temperature changes. On the other hand, there is such a marked resemblance between reactions to histamine and inflammatory reactions that one is reluctant to believe that the latter may not depend on the release of some histamine-like substance (H-substance). This same reasoning applies equally well to the responses to extreme heat or cold.

In this connection reference should be made to observations made by Menkin.[239] He has found that the subcutaneous injection of inflammatory exudates produces locally an immediate vasodilatation and increase in capillary permeability. The exudates evoke none of the reactions of histamine. Their action appears to depend partly on their electrolyte composition and partly on some amino acid not related to histamine.

When an arm is congested by partial obstruction of the veins and later the arterial supply is occluded, white spots, which contrast markedly with the

surrounding cyanosed areas, may develop in certain regions of the skin. These are known as *Bier's spots*. They develop more readily when the arm is cooled. It has been claimed that they do not appear if the arm is immersed in water at 36° C., but they certainly can be produced when the arm is placed in very hot water (at 41° C. or more). In fact, they may develop with changes in temperature in the absence of occlusion of any kind. Their cause is not known. Tentatively it may be supposed that they are produced by liberation of some vasoconstrictor substance in addition to vasodilator substances, but no adequate hypothesis has been advanced to account for the irregularity of their occurrence and distribution. They do not develop in an area affected by histamine injection, but may develop earlier than elsewhere in the region of a scratch.[267]

THE VENOUS CIRCULATION

Measurement of Venous Pressure.—Venous pressure may be measured directly by inserting into a vein a needle connected to a reservoir of saline (asepsis must be observed in human work) and determining the pressure at which no flow occurs in either direction. It may be measured indirectly by determining the pressure which causes venous collapse; a capsule connected to a water manometer is fixed over the vein and pressure is applied to this system by compressing a rubber bulb filled with air. The best modification of this method is probably that of Brahms, Katz and Schutz.[47] A glass capsule covered with a rubber ring is cemented to the skin over a vein in the hand. An electric torch is held against the palm and the transmitted light is watched in a darkened room. The collapse of the vein as the pressure is raised is readily seen.

Flow and Pressures in Venules and Veins.—The figures given in Table XII, page 338, demonstrate how the vascular bed narrows again in the veins. The effect of this is to increase the rate of flow. The bed remains so much broader than that of the arteries that there is little loss of pressure head from friction. In the venules the hydrostatic pressure is much below the colloid osmotic pressure of the plasma, the walls are thin, and some fluid interchange may take place. Water would be absorbed, but particles of low molecular weight and small size present in the blood stream at greater concentration than in the tissue spaces could diffuse out. Calculation indicates that the pressure gradient from the venous end of the capillary to the venule is about 2 mm. Hg and to the main vein 6 mm. (Table XII, page 338). By direct measurement the gradient to the venule is found to be some 3.3 mm. Hg (4.5 cm. H_2O) (Fig. 101, page 340). The pressure fall is certainly quite slight. In an individual lying down at rest the total pressure fall from the venous capillary to the entrance of the right auricle is probably of the order of 16 to 20 mm. Hg (from 16.5 to zero or −3.5 mm.). The pressure in the right auricle is only slightly above the intrathoracic pressure, which in turn is somewhat below atmospheric pressure. The pressure in the veins of the hand and arm at heart level is normally about 5 mm. Hg (7 cm. of water).

The pressure head is quite inadequate to return the blood more than some 25 cm. against gravity. To move the blood from the foot to the abdominal cavity in the standing position would require an increase in the capillary pressure of 37 mm. Hg (50 cm. water). Such a pressure would disorganize the fluid balance in the capillary. No such increase in pressure ever occurs under normal conditions except for brief intervals when an individual makes a great effort to stand at rest. Attention has been drawn to William Harvey's experiments on the action of the valves in the veins. Through their action,

motions of the muscles, which of necessity compress sections of the veins, massage the blood centrally, and so effectively reduce the venous pressure when the muscle relaxes. For the same reason any passively applied massage applied in any direction to a limb improves its circulation. The return of blood to the central vessels is facilitated in proportion to the work being performed by the muscles and in proportion, therefore, to the arterial inflow, for this in turn is regulated in accord with the metabolism by reflex and chemical control of the arterioles and capillaries. Even the pulsations of the arteries probably assist venous return through compression exerted on veins.

Gravity Effects and Tissue Fluid Pressure.—When the venous blood reaches the abdominal cavity, the conditions are different. The large venous trunks in the abdominal area have no valves. Any muscular pumping action exerted there cannot, therefore, prevent the development of gravity effects. The venous pressure at the lower end of the abdomen must be about 20 mm. Hg or more (20 to 30 cm. of blood). But the intraperitoneal pressure is not at the atmospheric level. Measurements by Overholt[245] showed that the intestinal contents act as a fluid mass; consequently in the vertical position the pressure at the lowest part of the abdominal cavity is that created by the mass above, while the pressure at the epigastrium is slightly subatmospheric. In quiet breathing the descent of the diaphragm in inspiration does not raise the pressure; a reciprocal relaxation of the abdominal muscles balances its effect. In fact, there may be even a slight fall in intraperitoneal pressure during inspiration. With deep inspiration there is, on the other hand, a marked rise.

Since with normal respiration the descent of the diaphragm exerts little or no pressure on the abdominal veins return of blood in this valveless area must depend on some other mechanism. A similar condition must hold within the spinal column, for there too the veins are without valves. In both areas the veins are contained in a cavity with fluid contents, a condition which may be compared with those in the foot when the leg is immersed in water. Under such conditions the venous pressure in the foot is raised by the effect of gravity on the venous column, and capillary pressure is raised equally (through arteriolar dilatation), but no edema results, for the pressure of the water on the tissues raises the tissue fluid pressure to an equivalent degree. Disorganization of the normal relationship between hydrostatic pressure in the capillaries and the colloid osmotic pressure of the blood plasma does not result from gravity effects when the individual is immersed in water (a point of possible clinical value in the treatment of edema). No mechanisms have to be provided to protect the organism against gravity effects in areas such as the peritoneal cavity and the spinal canal, which have fluid contents. Valves are necessary to assist venous blood in entering or leaving such cavities, but within the cavities themselves they are superfluous or even disadvantageous.

The conditions in the leg when the subject is standing in air are very different from those which obtain when he stands in water. If he makes an effort to inhibit muscular movements, the venous and capillary pressures are raised, but the tissue fluid pressure is little changed since the tissues are semisolid and no such transmission of fluid pressure occurs. An increased transudation of fluid takes place and the tissues swell, rapidly at first and more slowly later as the tissue pressure increases. The colloid osmotic pressure of the blood is also somewhat increased by the fluid loss and this diminishes

exudation. One other factor can assist in the adjustments: the veins and venules are engorged as the result of the increased pressure and the consequent increase in their cross-sectional area lowers the resistance to flow. When an arm is allowed to hang down and so become engorged, the velocity of blood flow is increased rather than decreased (Goldschmidt and Light[142]). This reduction of resistance to flow with engorgement is of importance surgically. It explains the clinical experience that ligature of a large arterial trunk is more readily followed by the development of adequate collateral circulation when the vein is also ligated (observations of Sir George Makins in the South African War) and also the efficacy of the treatment of thrombo-arteritis obliterans by venous ligation.[299] While all these factors tend to compensate for the effects of gravity, compensation is incomplete and swelling or some other change causes discomfort associated with a reflex tendency to engage in muscular contraction. Muscular contraction lowers venous pressure and allows capillary pressure to be reduced to normal level through arteriolar constriction.

When a limb is raised above the heart level, gravity assists venous return and tends to lower the peripheral venous and capillary pressures. This reduction, however, is minimized by the tendency of the veins to collapse and so to increase the frictional resistance to flow within them. These changes maintain the peripheral pressures close to their normal values. The pressures in the veins are normally measured when the vessel is at the level of the right auricle. In man this is assigned the arbitrary level of the midpoint of the anteroposterior diameter of the thorax opposite the costal angle (where the lower ribs join the sternum).

Since the venous system is an elastic one, more or less fixed in the connective tissue but not rigid, the right auricle cannot be expected to be the precise reference point for gravity effects. This is discussed by Clark, Hooker and Weed[74] who report experiments on anesthetized and dead animals. They find that the hydrostatic effects of gravity should be estimated from other reference points, which in dogs are cephalic (for the upper extremity) and caudal (for the lower extremity) to the heart to the extent of about 0.2 of the distance from the heart to the most distal part of the limb.

Respiratory Effects on Venous Pressure and Flow.—The heart is contained in the thorax where the pressure is subatmospheric. The effective filling pressure of the heart is, therefore, the difference between the pressure in the heart chambers (dependent on venous pressure) and the intrathoracic pressure. It is probably of the order of 5 to 10 mm. of Hg. During inspiration when the intrathoracic pressure is lowered, not only air but also blood is sucked into the chest. During expiration the reverse is true. If the intrathoracic pressure is markedly raised by blowing against a resistance, the venous blood is dammed back, the veins become engorged and venous pressure is raised. Vigorous movements of the diaphragm may aid venous return by raising abdominal pressure during inspiration. During forced respiration (as in exercise) this is probably an active factor, but in quiet respiration reflex inhibition of the abdominal muscles may be adequate to prevent any measurable rise in intra-abdominal pressure during descent of the diaphragm. Consequently during quiet respiration the "respiratory pump," which assists venous return, is dependent solely on the intrathoracic pressure changes.

Control of the Veins.—The contractility of the superficial veins is obvious. They are large and dilated when the skin is warm, contracted when the skin is cold. This contractility appears to be a function of all veins. The reactions

may be direct responses to a physical stimulus or to chemical changes produced by the physical stimulus; they may be demonstrated in denervated limbs. But nervous control is also present; immersion of one arm in cold water may induce reflex contraction of the veins in the other arm.

Many investigations of venous contraction have been made. Usually to exclude the effects of variations in internal pressure a section of vein has been separated from its vascular connections and the degree of constriction has been judged by the resistance offered to flow from a perfusing system.[120-122, 183] The veins of the hind leg are supplied by constrictor and dilator fibers through the sciatic; the former are dominant with strong, the latter with weak stimulation. The constrictor fibers are sympathetic in type; the dilators are of posterior root origin. Reflex dilatation can be produced by inhibition of vasoconstrictor tone, or by active dilatation. In the abdominal cavity venous dilatation mediated through the vagus appears to depend on fibers of a sensory type. Dilatation of the inferior mesenteric vein depends on similar sensory fibers of the twelfth and

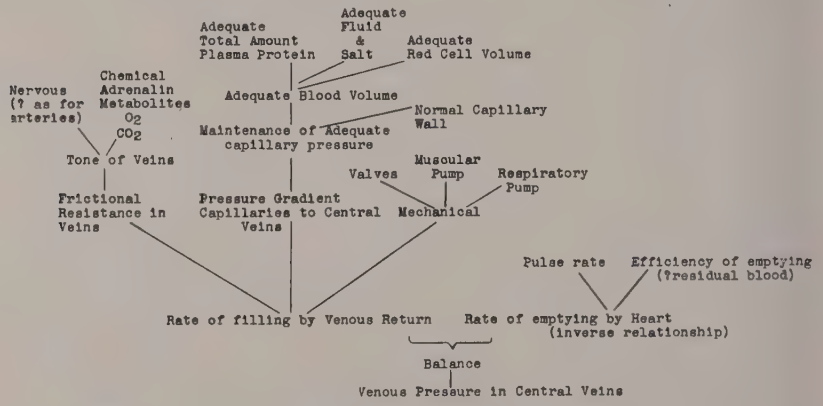


Fig. 176.—Outline of the factors which influence venous return to the heart.

thirteenth thoracic nerves.[183] The large intestinal veins are normally maintained in tonic contraction through the sympathetic. In a separated segment of such a vein Hooker[179] found a fall of pressure on section of the nerves or division of the cord below the medulla. The contraction is, therefore, under tonic control of the vasomotor center.

The veins, both small and large, contract under the action of adrenalin in both small and large doses. They dilate to histamine and acetylcholine in doses considered to be within the physiological range. The threshold concentrations for these reactions are: adrenalin, 1×10^{-8} (i.e., 1 in 100 million); histamine 1×10^{-12}; and acetylcholine 0.5×10^{-11}. High concentrations of both histamine and acetylcholine may give constriction.[121] The veins are probably involved in the direct vasodilatory effects produced by CO_2 excess and O_2 lack. In general the reactions of the veins to nervous and chemical stimuli appear to be similar to those of the capillaries.

Contractions of the veins undoubtedly cause variations in their reservoir capacity. Pressure waves, however, have been recorded in the valveless ab-

dominal veins which apparently are not mechanically dependent on either the cardiac or respiratory activity. These waves have been regarded[144, 177] as signs of muscular contractions of the wall which possibly have a propelling function.

The large amount of blood contained in the veins has already been pointed out (page 341). The venous return is particularly affected by changes in blood volume. As the result of the fluid balances in the capillary any deficit in blood volume tends to be made up by absorption of fluid. Any such absorption of fluid lowers the colloid osmotic pressure and with it the pressure at which balance takes place. The gradient for returning blood to the heart is consequently reduced. Serious symptoms may be generated, but unless there is extreme strain they may be prevented by active reflex adjustments. These reactions to changes in blood volume are complex and will be considered later, particularly in relation to hemorrhage.

The general relationships of the venous return, and the balanced forces that affect venous pressure are indicated diagrammatically in Fig. 176. This may be grouped with the series of diagrams already presented; it should be fitted in the uppermost left hand corner—see page 445.

CHAPTER XXXIII

THE REGULATION OF THE CIRCULATION

The various nervous and chemical effects that may influence the heart, arteries, capillaries, and veins have been outlined. The correlation of these effects to control the circulation as a whole must now be considered. In previous chapters we have considered the nervous and chemical agencies which affect cardiac output and blood pressure, but this is only one side of the story. Blood pressure and blood flow in their turn affect receptors of the nervous system and so induce a circle of events that modify and regulate both cardiac output and blood pressure. Chemical controls also exist and tend to increase the circulation in any area in which metabolites are being rapidly formed. These metabolites have direct effects on the vessels and, if they enter the blood stream, they also modify reflex responses by altering the sensitivity of the receptors and the reflex centers. They may also directly stimulate certain receptors.

The reflex adjustments of the circulation are of two types. One of these has the function of causing changes in the cardiovascular system when a change takes place in another part of that system. These responses originate within the system, and serve to maintain the coordination of one part with another. They may be termed *intrinsic* reflexes. They also regulate the whole system to prevent any sudden large increase or decrease in the capacity of the vascular bed, which would necessitate a sudden large change in blood volume. Under conditions of high venous inflow (e.g., exercise) the cardiac output is high and arterial pressure is allowed to rise considerably to maintain a rapid arterial flow. Under more moderate conditions the arterial pressure is maintained remarkably constant in spite of considerable changes in volume flow. The pressure is allowed neither to fall so low that there is not an adequate margin for overcoming the effects of gravity, nor to rise so high as to overload the heart. The second type of reflex adjustment has the function of distributing blood to various areas according to their needs. They satisfy the demands of special organs or parts and, so far as is known, originate in extravascular receptors. Accordingly they may be called *extrinsic* reflexes. These are concerned with the differential distribution of blood. As will be seen the two types of reflexes are not independent; regulation of the pressures within the system has to be subordinated to the metabolic needs of the tissues and the demands of the tissues can only be met if the vascular system is not taxed beyond its limit. Consequently, in many conditions one vascular reflex may be competing with others, both intrinsic and extrinsic, and the final effect is determined by many factors.

INTRINSIC REFLEXES CONTROLLING THE CIRCULATION

The Receptors and Sensory Paths

The regulation is attained mainly through reflex adjustments initiated by sensory impulses derived (1) from the heart and large veins through the vagus, (2) from the aortic arch through the aortic or depressor nerve, a branch of the vagus, and (3) from the bulbous junction of internal and external carotid arteries, the *carotid sinus* through the glossopharyngeal nerve (cranial IX). The

impulses pass to the medulla where they influence a center or centers which control both the cardiac rate and the degree of vasomotor activity. In this way the cardiac rate may be retarded or accelerated and the peripheral resistance decreased or increased.

Receptors sensitive to rises in arterial pressure in the arch of the aorta are innervated by a branch of the vagus nerve, the *aortic* or *depressor nerve* which was first described by Cyon and Ludwig in 1866. Similar receptors are situated in the *carotid sinus*, and are innervated by a branch of the glossopharyngeal nerve. The carotid sinus mechanism was described originally by H. E. Hering in 1924 and has been much investigated since that date. C. Heymans[170] has especially contributed to its elucidation. Both groups of receptors are thrown into activity by arterial distention. Further, there are present in the region of the aortic arch and carotid sinus other receptors which are sensitive to chemical

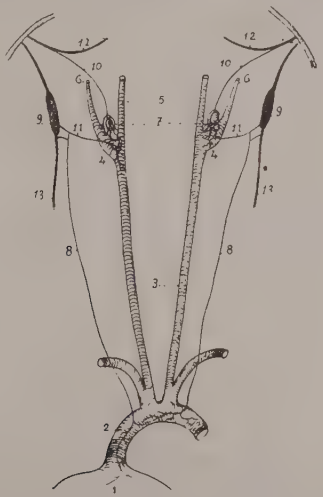


Fig. 177.—Innervation of the carotid sinus, carotid body, and arch of aorta. *1*, heart; *2*, arch of aorta; *3*, common carotid; *4*, carotid sinus; *5*, external carotid; *6*, internal carotid; *7*, carotid bodies; *8*, aortic or depressor nerve; *9*, ganglion of vagus; *10*, nerve branch connecting the carotid sinus with the glossopharyngeal nerve; *11*, nerve branch connecting the carotid sinus with the vagus ganglion; *12*, glossopharyngeal nerve; *13*, vagus nerve. (After C. Heymans.)

stimuli. These chemoreceptors are contained in separate organs called the carotid and aortic bodies. The *carotid body* is a glandular structure with a rich arterial blood supply which passes through in thin-walled sinusoidal vessels devoid of any muscular coat. The receptors appear to be affected by the unloading tension of oxygen in the arterial blood, as well as by other chemical factors including carbon dioxide. The *aortic body* is a similar structure embedded in the fatty envelope of the aortic arch. The sensory nerve fibers that supply the carotid body join the branch of the glossopharyngeal which innervates the carotid sinus. The nerve fibers from the aortic body pass centrally in part by branches which together with the recurrent laryngeal nerves join the vagi, probably also in part by branches which join the main trunks of the vagi (Schmidt and Comroe[279]).

In the rabbit the aortic nerve has the distribution indicated in Fig. 177; it enters the vagus by two branches, one joining the main trunk and one the superior laryngeal. The superior laryngeal nerve arises from the vagus close to, or together with, a branch which goes to the carotid sinus; only the latter is shown in the figure. In the cat the arrangement is similar, but the aortic nerve is very small and is often enclosed in the vagus sheath. In the dog and in man it is normally bound in the vagus sheath and is only recognizable where it branches to join the main part of the vagus and laryngeal. In the dog it may, however, be recognized as a separate bundle within the vagal sheath.

The carotid sinus is a localized enlargement of the carotid at its bifurcation. Fibers from the glossopharyngeal as well as from the vagus join it. The former appear to be the ones chiefly concerned with the vascular reflexes.

Other receptors which appear to react to distention are present in the walls of the large veins, auricles, and possibly also in the ventricles. Their nerve fibers pass centrally in the vagi. Pacinian corpuscles are also probably concerned in vascular reflexes.

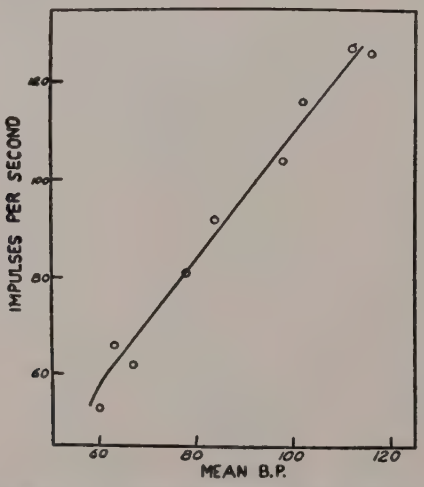


Fig. 178.—Frequency of afferent nerve impulses from three receptors in the carotid sinus at different arterial pressures. (From Bronk and Stella: J. Cell. and Comp. Physiol. 1: 113, 1932.)

Woollard[325] has found that Pacinian corpuscles sometimes lie in close contact with the wall of an artery and are supplied by a branch of a nerve fiber which also sends a branch along the arterial wall. These sensory structures lie in close contact with the mesenteric arteries, and are found in large numbers in the pancreas. Characteristically they are surrounded by a network of small vessels and are penetrated by a vessel which breaks up into capillaries within them (Ruffini).

It is probable that other vascular receptors exist and possible that some receptors serve both vascular and other sensations. Matthews[234] has demonstrated that muscle spindles may sometimes be stimulated by the pressures generated in a muscle with each pulse beat.

The nature of the effective stimuli and the character of the sensory impulses generated are similar in the case of all these receptors. In the pressure-sensitive areas of the aorta and carotid sinus volleys of impulses are generated which vary in frequency with the degree of intra-arterial pressure.[52] The thresholds of the different sense cells vary; consequently the higher the pressure the greater the number of fibers stimulated and the higher the frequency of impulses in

each fiber (Fig. 178). The whole picture of a pulse wave may be reflected in the spacing of successive impulses (Fig. 179). The magnitude of the pulse pressure is a factor of importance in determining the extent of stimulation, for the response is greatest when pressure rises suddenly. If the pressure is maintained at a high but constant level, the frequency of the impulses decreases (adaptation of end organs) but does not fall to zero. On the other hand, if the pressure is suddenly dropped, all impulses may cease for a brief period. In the relatively little adaptation which they show these receptors resemble muscle proprioceptors (see page 68).

There is available no convincing evidence that any receptors of the carotid sinus and aortic arch are stimulated by a low arterial pressure per se. The very marked reflex changes (vasoconstriction and cardiac acceleration) which occur when the pressure falls below a normal level within these parts of the vascular system are due to *cessation* of receptor stimulation. It is perfectly clear from the work of Bronk (see Fig. 178) that at normal arterial pressures

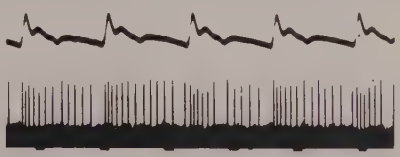


Fig. 179.—Relation of the frequency of afferent impulses from a single carotid sinus receptor to the pressure curve of the pulse. The upper record is of blood pressure (Wiggers manometer). Below is the oscillograph record of action potentials in the nerve fiber. On the undersurface of this record time is indicated in one-fifth second. (From Bronk and Stella: J. Cell. and Comp. Physiol. **1**: 113, 1932.)

Fig. 180.—Discharge of afferent impulses from several Pacinian corpuscles synchronous with pulse. The uppermost record is the pulse. In the middle is an oscillograph tracing of nerve impulses in a few afferent fibers of the splanchnic nerve. The lowest record is time in one-fifth second. (From Gammon and Bronk: Am. J. Physiol. **114**: 77, 1935.)

afferent impulses from these receptors are continually bombarding the vasomotor and cardiac centers in the medulla. Their activity is tonic in the same sense that vasoconstrictor discharge is tonic. Since their central action (see below) is to evoke a reflex diminution of vasoconstrictor discharge and a reflex slowing of the heart their cessation produces the opposite effects. This interpretation is supported by the fact that bilateral section of the aortic and carotid sinus nerves produces exactly the same effects as lowering the pressure within the vessels in whose walls they have their origin.

The impulses from the Pacinian corpuscles differ somewhat from those of the carotid sinus and aortic nerves.[134] There is a similar tendency for the impulses to be most frequent at the peak of the pulse curve (Fig. 180), but the frequency appears to vary more with the fullness of the vessels than with the internal pressure. They may be stimulated at low pressures if the vessels are dilated and the pulsations large.

Reaction to Changes in the Tension of Oxygen and Carbon Dioxide.—In the *carotid body* receptors which are sensitive to chemical changes react to oxygen lack, and to a less extent to CO_2 excess. Their anatomical situation is different from that of the pressure receptors. Similar receptors are present in the aortic body. Records of action potentials in the nerve fibers which connect them with the central nervous system have been obtained. It is said that the receptors sensitive to CO_2 excess react only when the tension of this gas exceeds 32 mm. Hg; they show very little adaptation.[270]

Responses to Variations in Arterial Pressure

These reactions may be investigated by several methods. The central end of one aortic nerve may be stimulated to mimic the response to a rise in arterial pressure, and in this way the mechanical effects of an actual rise in pressure may be avoided. The effect produced by such stimulation is greater if the other aortic nerve and the nerves from the carotid sinuses (together these nerves are often called the *buffer nerves*) are divided to avoid opposing reflexes set up through them when the pressure falls.

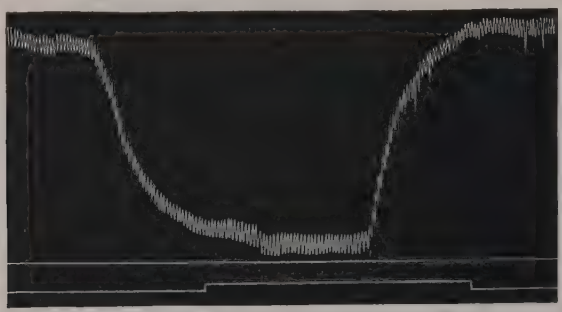


Fig. 181.—Fall of blood pressure from excitation of the aortic or depressor nerve. The drum was stopped in the middle of the curve and the excitation maintained for seventeen minutes. The base line indicates a pressure of 60 mm. Hg and the scale is 2 mm. Hg per 1 mm. excursion. Record to be read from right to left. (From Bayliss.)

The fall in mean arterial pressure (depressor reflex) that results from stimulation of the central end of an aortic nerve, without section of the other buffer nerves, is shown in Fig. 181. The pressure falls at once and remains at a low level as the stimulus is continued. Plethysmographic records show that the fall is associated with an increase in the volume of the limbs and viscera; it is associated, therefore, with a general vasodilatation. The change may be produced, as in this case, with little alteration in pulse rate or (as may be demonstrated if the blood pressure is recorded with a membrane manometer) in pulse pressure (usually a slight increase is present). It is evident that the response need not entail any considerable change in cardiac output. According to Heymans,[170] measurements of venous return to the heart made by the Rein method indicate some reduction in output. The fall of pressure is dependent, therefore, mainly on a great reduction of peripheral resistance. This could only occur as a result of arteriolar relaxation. The capillaries are also probably dilated, for McDowall[224] reports that the fall of pressure produced by histamine becomes less during stimulation of the aortic nerve. The large veins

are also dilated.[120] The dilatation apparently involves all three types of vessels in many different areas. Venous pressure is reduced in some animals, changed but little in others.[224] The pulse rate is sometimes slowed. The enlargement of the vascular bed by the general involvement of all types of vessels causes the fall in venous pressure and reduction in cardiac output. The work imposed on the heart is decreased. The reaction may be augmented by a decrease in secretion of adrenalin (Richards and Wood[257]) and by a relaxation of blood reservoirs, such as the spleen.

A similar depressor reflex is evoked by raising the pressure within the carotid sinus or by stimulating the sinus nerves. Heymans[170] has investigated this response in great detail and some examples of his procedures and results will elucidate the important mechanism involved.

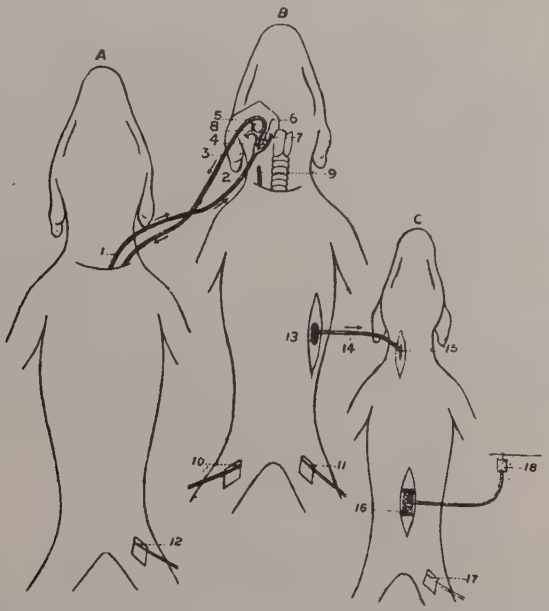


Fig. 182.—Schema of perfusion of the isolated carotid sinus of dog *B*, by dog *A*, and an anastomosis between the adrenal vein of *B* and the jugular vein of dog *C*. *1*, left carotid artery of dog *A*; *2*, right carotid of *B* anastomosed with carotid of *A*; *3*, left external jugular vein of *A*; *4*, isolated right carotid sinus of *B*; *5*, lingual artery of *B*, anastomosed with jugular vein of *A*; *6*, nerve supply to carotid sinus of *B*, *10*, *11*, *12*, and *17*, femoral arteries to manometers; *13*, *14*, and *15*, adrenal-jugular anastomosis; *16*, spleen in plethysmograph connected with volume recorder, *18*. (After C. Heymans: Arch. internat. de pharmacodyn. et de thérap. 35: 269, 1929.)

In the experiment to be cited the isolated carotid sinus of a dog (Fig. 182, dog B) was perfused from a second dog (dog A). The nerves were preserved. In the simpler type of experiment the third dog (dog C), shown in the figure, was not used. An intravenous injection of adrenalin in dog A raised its arterial pressure and increased the distention of the carotid sinus of B. This produced a reflex fall in arterial pressure in dog B and a slowing of its pulse from 160 to 110 (Fig. 183). For more detailed analysis three dogs were employed (Fig. 182). In this experiment the vein from one adrenal gland of dog B was connected with the jugular vein of dog C, so that its adrenalin output could only be discharged into that

animal; the other adrenal was removed. Secretion of adrenalin in dog C was excluded by removal of both glands. The spleen of C, inserted in a plethysmograph so as to record volume changes, was ready as an indicator of adrenal secretion in dog B. A record obtained with this arrangement is shown in Fig. 184. A fall in pressure in the carotid sinus of dog B was produced by clamping the artery from dog A at the times marked *a* and *c;* the pressure was returned to normal by removing the clamp at *b* and *d*. At *e* the pressure was raised within the sinus by injecting adrenalin into dog A. The experiment demonstrates that the arterial pressure in B is increased when the pressure in the sinus falls and vice versa, that variations in adrenalin output are not essential for these changes in dog B, but that an increase in adrenalin output accompanies the reflex rise of pressure and may produce changes in dog C, that splenic contraction may be induced by the increase in adrenalin, and that it accompanies and can assist in the production of the pressure rise.

The reaction to a fall in pressure in the carotid sinus involves: (1) an increase in peripheral resistance, probably involving constriction in all types of vessels, (2) an increase in pulse rate, (3) increased output of adrenalin, and

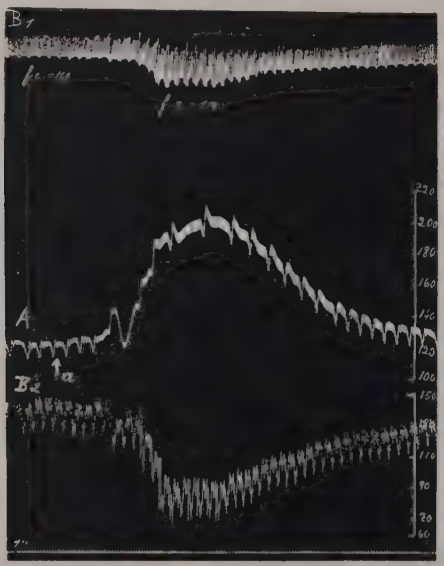


Fig. 183.—Records obtained in the experimental arrangement shown in the previous figure. A rise in pressure in donor dog *A* produced by injection of adrenalin (*a*) causes a fall in pressure in recipient dog *B*. *A*, mercury manometer tracing of arterial pressure in dog *A*. Two tracings of pressure in dog *B* are shown: B_1 with membrane manometer, B_2 with mercury manometer. (From Heymans: Arch. internat. de pharmacodyn. et de thérap. 35: 269, 1929.)

(4) emptying of blood reservoirs with contraction of the large veins. The reaction increases blood pressure, both arterial and venous. Unless the resistance is too great the cardiac output is probably increased. In general, the response is the opposite of that produced by stimulation of the aortic or sinus nerves.

The Reciprocal Nature of the Responses.—In attaining these cardiac and vascular adjustments the efferent nerves work in a reciprocal manner. When the pulse is slowed, the main effect is produced by increased activity in the vagi, which by their peripheral action inhibit the heart. After vagotomy the change

in pulse rate is quite small, but the accelerators certainly play a role in the slowing of the heart produced by an increase in pressure in the carotid sinus. It can be shown that under these circumstances the tonic accelerator discharge is diminished (Fig. 185). Thus increased activity of the vagi is accompanied by decreased activity of the sympathetic and vice versa. The same relationship probably holds for the vasomotor changes. This was particularly emphasized by Bayliss.[27] Vasodilatation on peripheral stimulation of the posterior roots was described by Stricker (1876) whose results were confirmed by Bayliss[26] (see Fig. 172). Bayliss[27, 29] showed that even after removal of the abdominal sympathetics reflex dilatation in the hind limb occurs when the aortic nerve is stimulated (Fig. 186). Apparently the posterior root vasodilator neurons are reflexly excitable. He also showed that a similar dilatation can be demonstrated in the salivary gland on aortic nerve stimulation even when the vasoconstrictor supply (the cervical sympathetics) had been cut. This must mean that dilatation can also be induced reflexly through the chorda tympani.

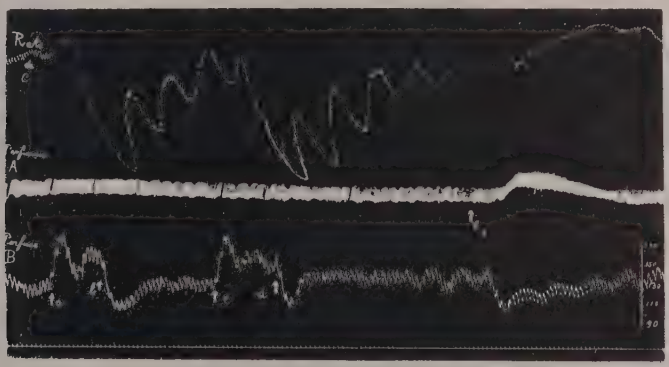


Fig. 184.—Records of arterial pressure in donor dog *A* recorded with a membrane manometer (*A*), in recipient dog *B* with a mercury manometer (*B*) and volume of spleen (rate) of dog *C* (downward stroke indicates decrease in volume). Description of experiment in text. (From Heymans: Arch. internat. de pharmacodyn. et de thérap. 35: 269, 1929.)

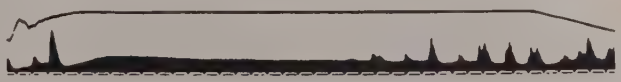


Fig. 185.—Reflex inhibition of the tonic discharge of impulses in fibers of the sympathetic cardio-accelerator nerves by distention of the carotid sinus. Upper record, pressure in the sinus. Lower record, oscillograph tracing of action potentials in the accelerator nerve. (From Bronk: The Harvey Lectures, 1933-34, Baltimore, 1934, The Williams and Wilkins Co.)

Reflex vasodilatation can be effected most markedly by inhibition of vasoconstrictor tone. Thus in the experiment illustrated in Fig. 187 all nervous connection between the medulla and the posterior root fibers going to the lower limb were excluded by section of the spinal cord at the third lumbar segment. On stimulation of the central end of the vagus (with the included aortic nerve) there was a marked fall of pressure and an increase in limb volume (first stimulation). After this the abdominal sympathetic chains were cut. Then, on repetition of the stimulus the volume of the limb decreased; it followed passively the changes in blood pressure. The control of the vessels, therefore, appears

Fig. 186.—Record showing that stimulation of the aortic nerve causes a reflex discharge over vasodilator nerves. Upper curve, volume of hind leg of dog. Lower curve, arterial pressure. Before the experiment the vasoconstrictor supply to the leg was interrupted by section of lower abdominal sympathetic chains. The signal marks stimulation of the central end of the vagus. With the drop in arterial pressure there was an increase in leg volume. This reflex dilatation was abolished by section of the spinal cord at the second lumbar segment, a procedure which separated the vasomotor center from the spinal origin of the limb vasodilators. (From Bayliss: J. Physiol. 28: 276, 1902.)

Fig. 187.—Record showing that stimulation of aortic nerve (upper signal) evokes vasodilatation by reflex inhibition of the tonic discharge of impulses over vasoconstrictor nerves. Arterial pressure below, limb volume above. Spinal cord transected at third lumbar segment to disconnect dilator nerves of posterior root origin. Record at left: stimulation produces increase in leg volume with decrease in arterial pressure. Record at right obtained after section of vasoconstrictor fibers to the leg; stimulation still produces a fall in arterial pressure but the leg follows the pressure passively instead of dilating. (From Bayliss: Proc. Roy. Soc. B. 80: 339, 1908.)

also to be arranged in a reciprocal manner. Bayliss' diagrammatic representation of his viewpoint is given in Fig. 188.

These observations by Bayliss, which indicate participation of reflexes through efferent impulses over posterior roots, receive some substantiation from the description of pressor and depressor reflexes in sympathectomized animals.[249] The presence of reflex responses from the carotid sinus in such animals would be conclusive. The occurrence of such reflexes has been described, denied,[297] and reaffirmed.[16] The question remains controversial. Whether vasodilators of sympathetic type are normally involved in these intrinsic reflexes is uncertain. Ergotoxine appears to paralyze vasoconstrictor sympathetic responses and to leave the vasodilator fibers relatively unaffected, but Wright[327] was unable to demonstrate reflex vasodilatation in response to aortic nerve stimulation after ergotoxine. He considers that the central nervous system was also modified.

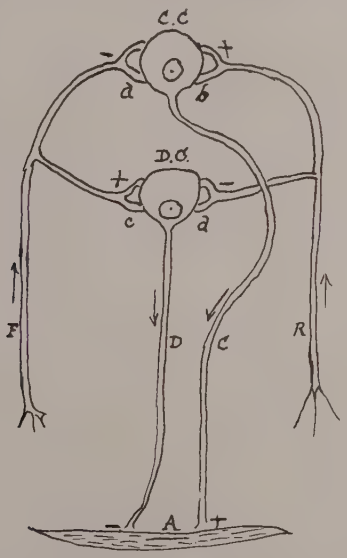


Fig. 188.—Diagram showing the probable arrangements of the vasomotor reflexes.

A. Muscle of arteriole.

D. Vasodilator nerve fiber terminating on *A* and inhibiting its natural tonus, as indicated by – sign.

C. Vasoconstrictor fiber also ending in *A*, but exciting it (+). These two kinds of fibers arise from the dilator center (*DC*) and the constrictor center (*CC*), respectively.

F. Afferent depressor fiber, dividing into two branches, one of which (–) inhibits the constrictor center, while the other (+) excites the dilator center causing dilatation of the arteriole and fall of blood pressure.

R. Pressor fiber exciting *CC* and inhibiting *DC*, and therefore causing vasoconstriction and rise of blood pressure.

a, *b*, *c*, and *d* represent the synapses of the pressor and depressor branches with the efferent neurons. (From Bayliss: Proc. Roy. Soc. B. **80**: 339, 1908.)

The responses to carotid sinus stimulation can be demonstrated, though not analyzed, more simply. In an animal anesthetized with chloralose, which leaves these reflexes very active, clamping the two carotids below their bifurcations (and thus lowering the pressure in the sinuses) induces a marked increase in arterial blood pressure. If an intravenous injection of adrenalin be given a marked increase in blood pressure with increase in pulse rate results from the direct effect of the adrenalin, but, at the height of the pressure rise, the heartbeat may be very greatly slowed. In this slowing heart block may be a factor. The very great change in pulse rate may depend on the summation of stimulation effects from all four

buffer nerves. Similar changes in pulse rate may be seen on stimulation of the splanchnic nerve in the anesthetized animal. These contrast with the simpler secondary pressure rise with cardiac acceleration from adrenalin obtained in a decapitate cat. The marked cardiac inhibitions obtained in an intact animal disappear when the vagi are cut. To exclude the possibility that they may depend on variations in the actual blood supply to the medullary centers Heymans[170] used the method indicated in Fig. 189. The general arrangement is the same as that of Fig. 182, but dog A perfuses both carotids of dog B, in which the head is isolated so that it is connected with the trunk only by the spinal cord. One of the two carotid sinuses is denervated; the nerves of the other are left intact. Clamping the carotid passing to the innervated sinus gave responses similar to those already described, while clamping the other artery, though producing the same effect on cerebral flow, induced no such responses. Variation in the cerebral flow is not, therefore, a major factor in producing results of this type.

Fig. 189.—Schema for perfusion of the head of dog *B* by dog *A*. The head of dog *B* is attached to its own trunk only by the spinal cord. Dog *C*, adrenalectomized, receives the blood from the adrenal of dog *B* by 6-7, an adrenal-jugular anastomosis. *8*, spleen of dog *C* in plethysmograph connected with piston recorder. *9*, *10*, *11* and *12*, femoral arteries attached to manometers. (After C. Heymans: Arch. internat. de pharmacodyn. et de thérap. 35: 269, 1929.)

Bilateral division of the carotid sinus and aortic nerves permanently raises the blood pressure. The heart rate is also increased and is usually almost as rapid as it is following section of both vagi. Tonic vagal inhibition is almost absent, and the sympathetic supply to the heart is unbalanced and possibly overactive. The heart hypertrophies. Extrasystoles, both auricular and ventric-

ular are common; they often occur in groups and the electrical changes may be abnormal in type. These effects are due to an absence of the tonic afferent impulses from the two regions.

As already pointed out there is no evidence that under physiological conditions afferent impulses are set up by a fall in arterial pressure. When the pressure in the carotid sinuses falls very low, below 50 mm. Hg, a paradoxical stimulation of low pressure may develop, so that decreasing the pressure in the sinus decreases the blood pressure instead of increasing it. The response at this level is then the exact opposite of the normal. Heymans[170] considers this due to stimulation of the receptors by deformation through collapse of the walls of the sinus.

Responses to Variations in Venous Pressure

Receptors in the auricles and probably in the large veins appear sensitive to distention in these areas. If the venous pressure be raised by intravenous infusion, the pulse rate is increased (the Bainbridge reflex). This occurs in spite of the fact that such infusions also tend to raise arterial pressure, which in turn induces reflexes slowing the heart. If venous pressure is lowered there is a tendency for the heart to slow, but, if the arterial pressure falls, this effect is antagonized by a cardio-accelerator reflex set up by decreased impulses from the arterial system. Changes in venous pressure may also produce reflex vasomotor effects (the MacDowall reflex). If the venous pressure be lowered by hemorrhage, section of the vagi may produce a considerable additional fall of pressure. This may indicate the presence of sensory fibers in the vagi which can reflexly stimulate an increased vasoconstrictor tone. Decreased venous distention induces vasoconstriction. These two reflexes, described by Bainbridge[18] and MacDowall,[224] respectively, form on the venous side the counterpart of the arterial reflexes. They should function to prevent circulatory failure, due either to inadequate venous return, or overdistention of the heart in diastole from too great a rise of venous pressure. Some workers have been unable to confirm the existence of these reflexes, but the depth of anesthesia used may account for such failures. Their existence and importance are supported by the bulk of the evidence available.

Intrinsic Reflexes From Other Receptors

It is possible that the Pacinian corpuscles also aid in maintaining standard conditions in the vascular system. Though stimulated by changes within the vascular system, they may serve to regulate the differential distribution of blood. When an individual stands up after lying down, the arterioles in the foot must be considerably constricted to guard the capillaries from the very great increase in arterial pressure caused by the effect of gravity. Receptors of the Pacinian type may play a part in this type of response. The fact that a single nerve fiber may supply both the arterial wall and a Pacinian corpuscle suggests that it may take part in an axon reflex.[325]

At one time the aortic and carotid receptors were believed to be the only sensory receptors concerned in these intrinsic cardiovascular reflexes. It now seems likely that there are many others. Heymans and his collaborators[171] have described reflex adjustments in the vascular system in spinal animals where all connections of the aorta and carotid body with the central nervous system were excluded. The reflex changes were produced in response to changes in arterial pressure. They may have been due to impulses from receptors of the Pacinian corpuscle type acting on centers within the spinal cord, or other as yet unidentified receptors may be concerned.

Reflex responses from the chemically sensitive carotid and aortic bodies have been mentioned. It is probable that other chemically sensitive receptors exist. Possibly the coccygeal body is an intrinsic receptor of this type. Certainly receptors sensitive to chemical changes exist in the muscles; these presumably should be classed as extrinsic receptors. The reac-

tions from the carotid and aortic bodies have profound effects not only on the circulation but also on the respiration. The responses to chemically sensitive receptors are consequently considered later (page 476).

EXTRINSIC REFLEXES; THE DIFFERENTIAL DISTRIBUTION OF BLOOD

The distribution of blood in accord with the needs of different tissues may be, and probably is, very largely dependent for its maintenance on chemical stimuli. Reflex responses also play a considerable rôle, particularly in assisting rapidity of response. These reflexes have this general pattern: they cause vasodilatation in an active or stimulated area and vasoconstriction in other areas. In most cases the arterial blood pressure is raised. They are, therefore, grouped as pressor reflexes. The effect on different areas is *reciprocal*; dilatation in one area is accompanied by constriction in others and

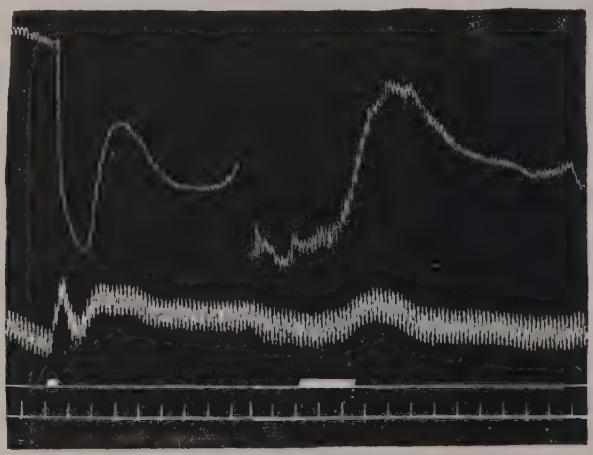


Fig. 190.—Lovén reflex (at right) in which a better blood flow to a part is brought about by a reflex local vasodilatation which occurs at the same time that arterial pressure is reflexly raised by a general vasoconstriction. Upper curve, volume of hind leg of dog; lower curve, arterial pressure. Vasodilators to leg in the posterior roots were cut off by section of lumbar and sacral dorsal roots. At left stimulation of central end of cut median nerve produced a reflex vasoconstriction in which the leg vessels participated (volume decreased with rise in pressure). At right stimulation of the central end of a sensory root of the leg (sixth lumbar dorsal root) caused a reflex rise in pressure, but the vessels in the limb itself dilated (volume increased). (From Bayliss: Proc. Roy. Soc. B. 80: 339, 1908.)

in each the involvement of constrictor and dilator mechanisms is again probably on a reciprocal basis. This type of response was first described by Lovén in 1866 and sometimes bears his name. An example from Bayliss' beautiful analysis[27, 29] is shown in Fig. 190. In the first record the central end of a nerve in the foreleg (the median) was stimulated. This caused a pressor response in which the hind leg participated. The vasoconstriction there was mediated through the sympathetics, for the posterior roots had been divided. In the second record from the same experiment, the central end of one of the cut sensory roots supplying the lower limb was stimulated. Again there was a pressor response, but the local effect on the limb, from which the nerve arose, was a reflex dilatation through inhibition of the normal vasoconstrictor

tone. The sensory nerves involved in such stimulation no doubt include pain fibers and probably fibers from muscles. The local vasodilatation brought about in the manner just described may be an experimental elicitation of a response which accompanies inflammation and muscular activity. If the sensory nerves from a limb be excited with weak stimuli at low frequencies a depressor effect, rather than a pressor one may be obtained. In this case a local dilatation is probably induced with little or no constriction in other areas. The pressor responses are obtained only if the stimuli are about 33 times as strong as those required to induce a depressor response or spinal muscular reflex. Possibly the depressor responses are elicited from muscle receptors and the pressor ones from pain receptors.

The sensory nerves contain slowly conducting fibers, probably small nonmyelinated fibers of high threshold, which probably mediate the dull aching pain of inflammation. It has been shown by Clark, Hughes and Gasser[69] that the larger fibers in a nerve trunk are the ones most readily rendered inactive by oxygen lack. Thus after a period of circulatory occlusion strong stimulation of a mixed nerve activates only smaller fibers. Under such conditions stimulation of a sensory nerve produces a fall in arterial pressure which is profound, long maintained, and shocklike in character. Its intensity is such as to suggest a general vasodilatation. It is of interest that in man a very similar reaction may accompany the dull aching pain caused by puncture of a fascia or an artery. This reaction involves a slow pulse, low blood pressure, sweating, and long-continued after-effects. Some types of surgical shock may be related to it (see page 524).

The sensory origin of cardiovascular reflexes evocable from muscles is probably quite complex. In response to exercise there is a rapid dilatation of vessels supplying muscles. There is probably an immediate reflex dilatation induced by impulses from the muscular proprioceptive receptors. Dilatation also certainly results from the direct effect of metabolites on the vessels. In addition, reflex vascular effects can apparently be produced from muscle receptors which are sensitive to chemical stimuli. It has been shown[5, 6] that considerable increases may be induced both in pulse rate and blood pressure if a muscle be exercised while the local circulation is occluded by an inflated Riva-Rocci band. If extensive work is performed under such circumstances, pain is produced, but the reflex changes in the circulation are induced with degrees of exercise far below those which give pain. Since the changes in the circulation develop outside the occluded area, they must have a reflex origin. The reflexes appear to be due to chemical stimulation of receptors, for they continue after conclusion of the exercise until the occluded circulation is released. As soon as the muscular tissue has received an adequate amount of circulating blood the reactions disappear. There is some evidence that reactions of a similar type may involve reciprocal reflex adjustments in blood vessels supplying tissues in the neighborhood of active muscles.

THE CENTRAL CONTROL OF THE CARDIOVASCULAR RESPONSES

The central mechanisms which control and regulate the various cardiovascular reflexes may be regarded as portions of the central representation of the autonomic system (see Chapter XVI). The most essential cardiac and vasomotor centers are situated in the bulbar and pontile portions of the brain stem. A transection which separates the mesencephalon from the rhombencephalon, i.e., one made at the level of the rostral border of the pons, does not in any way impair the cardiovascular responses to stimulation of

sensory nerves nor does it lessen any of the tonic discharges. Some unpublished work by C. B. Thomas has shown that not only after removal of all cerebral cortex but also after low mesencephalic transection of the brain stem, lowering or raising the pressure in the carotid sinus produces responses which are as great as, or even greater than, those elicited in precisely the same manner just before the central intervention. This finding contradicts an assumption which has often been expressed, namely, that the hypothalamus contains a central mechanism essential for these reactions. It must not be concluded, however, that higher portions of the brain do not exert influences on the heart and blood vessels. Indeed there is much evidence that not only the hypothalamus but also certain regions of the cerebral cortex may exert quite definite effects on many visceral effectors, among them those of the cardiovascular system (see page 186).

When the bulbar centers receive the various groups of afferent impulses (pressor and depressor) they respond by increased or decreased activity. Some portion of the visceral motor nuclei of the vagus nerves contains the cell

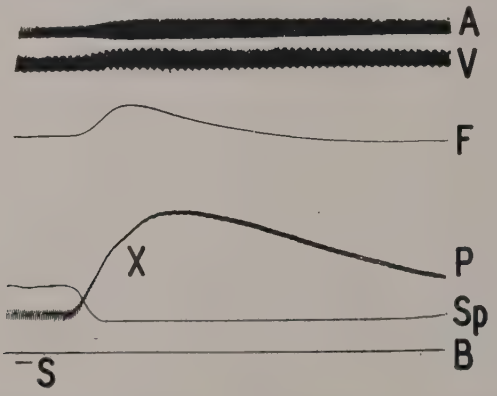


Fig. 191.—The effect of stimulation of the central end of a cut splanchnic nerve in a dog in which the thoracic cord had been cut some weeks earlier. The lowest line is a signal, *S*, indicating the time of the stimulation of the nerve and the continuous line, *B*, above it is the base line of the arterial pressure record. Above this is a record of arterial pressure (mercury manometer), *P*, which shows a pronounced reflex rise in pressure. This rise was accompanied by a reflex contraction of the spleen (*Sp*) and a passive increase in the volume of the foreleg, *F*, since this was separated by the transection from the part of the cord mediating the reflex. The two uppermost records indicate the contractions of the auricle, *A*, and ventricle, *V*. The blood pressure record shows a secondary rise, *X*, forming a step in the curve. This latter rise was due to adrenalin secretion and was accompanied by an increased pulse rate and an increased force in the auricular and ventricular contraction which may be seen in the uppermost curves. The adrenalin was inadequate to diminish the volume of the foreleg in the presence of the higher pressure. (An unpublished record furnished by Sir Charles S. Sherrington.)

bodies of the cardio-inhibitory preganglionic (parasympathetic) neurons. These are tonically active and their discharge is subject to reflex inhibition and reflex augmentation. Somewhere in this bulbar complex is a group of cells which send impulses to the upper thoracic segments of the cord where they are relayed to the heart over the accelerator neurons (pre- and postganglionic sympathetic fibers). The bulbar origin of this pathway is also tonically active and subject to reflex excitation and inhibition. Very similar in arrangement to the nervous channel just described is one which carries impulses to the vasoconstrictor (sympathetic) outflow from the entire

thoracolumbar region of the cord. That this pathway discharges tonically is shown by the profound drop in arterial pressure (to 40-50 mm. Hg) which immediately occurs when the spinal cord is transected at any level between the medulla and the upper thoracic segments. This tonic discharge is readily modified reflexly to produce either vasodilatation (by central inhibition) or greater vasoconstriction (by central excitation). As already pointed out, vasodilator nerves show little or no tonic activity. Their central control is poorly understood, but it may be assumed that it is closely associated, both anatomically and functionally, with the central vasoconstrictor mechanism.

The bulbar mechanisms concerned in the control of vasoconstrictor and vasodilator discharges are referred to as the *vasomotor center.* An anatomical division of this into vasoconstrictor and vasodilator components has not been achieved. In view of the reciprocal relations of the two mechanisms and the fact that a general reflex vasodilatation is readily evoked by inhibition of vasoconstrictor tone, there is little reason to draw a distinction on physiological grounds.

A normal level of arterial pressure is found in the spinal animal after it has recovered from spinal shock (see page 185). That this is due to a tonic vasoconstrictor discharge of spinal origin is shown by the large drop in arterial pressure which ensues upon section of the splanchnic nerves or removal of the sympathetic chains. In the acute spinal animal no vasomotor reflexes or only very weak ones can be obtained by sensory stimulation below the level of the transection. After some time, when recovery from spinal shock has taken place, stimulation of sensory fibers produces marked pressor responses with evidence of increased output of adrenalin. An example is shown in Fig. 191. These facts indicate that there are spinal vasoconstrictor mechanisms (''centers''), apparently subsidiary to the bulbar centers, but capable in the spinal animal of independent activity. Whether the initial condition after transection, the final condition, or some intermediate stage represents the part normally played by these spinal centers in vascular responses is unknown. Comparison with other reflexes suggests that the third alternative is the most probable.

COORDINATION OF THE REGULATING MECHANISMS

Reflex Regulation.—The various intrinsic and extrinsic reflexes are correlated. It has been shown that, if an animal is subjected to a small hemorrhage, the blood pressure tends to fall, but reflex mechanisms keep this fall as small as possible. Rein and Rössler[255] have found that if the animal is warm and an active skin circulation for cooling is necessary, the adaptation is made by constriction of the intestinal vessels; the limbs are scarcely affected. If, on the other hand, the animal is cold the adjustments are made almost entirely by alterations in the flow to the limbs; the intestinal vessels are relatively unaffected (Fig. 192). In these experiments the variations in the differential distribution of blood were determined by the thermostromuhr method.

Reaction to hemorrhage involves a rapid pulse rate even though venous pressure is low. This response may depend partly on the effect of the fall in arterial pressure on the buffer nerve system. Since the increase in pulse rate may occur without any fall in arterial pressure this is probably not the only cause. A similar rapid pulse may accompany circulatory failure from dehydration after prolonged heating even though systolic pressure and pulse pressure

are above normal. That the reflex responses to low venous pressure are complex is indicated by the marked motor restlessness which accompanies a subnormal venous return. Hemorrhage, shock, and dehydration in man are all accompanied by this restlessness, which is hard to control. It disappears when the venous return is augmented by giving fluid. Diminished venous return appears to induce reflexly in man muscular movements that constitute the muscular pump mechanism.

The presence of other factors is also indicated by the circulatory changes in severe exercise. Here the arterial blood pressure may be raised, but the buffer nerves do not slow the pulse. Their activity is counteracted by other mechanisms, of which venous distention may be one. Probably chemical factors play a large part in such coordination.

Chemical Regulation.—Chemical factors can act in several ways. Metabolites acting locally may produce dilatation. Carbon dioxide, products of oxygen lack and histamine-like substances seem to be concerned. Adrenalin also may act, not so much as a regulator of the pressure in the arterial system, as by effecting the differential distribution of blood into areas where the acidity is

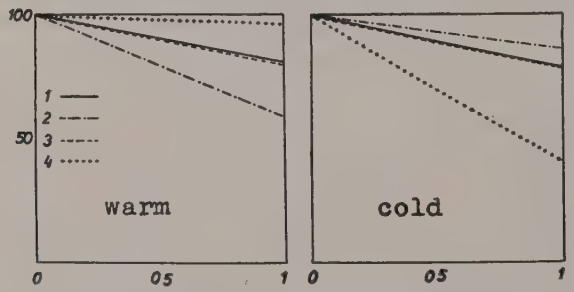


Fig. 192.—Percentage change in blood pressure and flow through different vessels in the same animal as the result of bleeding. Ordinates indicate the percentage change, abscissae the amount of hemorrhage in per cent of body weight. Room temperature, 35° (at left) and 18° (at right). *1*, blood pressure; *2*, blood flow through intestines; *3*, blood flow through kidney; *4*, flow through hind leg. (From Rein and Rössler: Ztschr. f. Biol. 89: 237, 1929.)

highest, and into areas, such as the muscles, where the vasoconstrictor effects of adrenalin are less readily obtained than the vasodilator. A most pronounced vascular effect may be induced by adrenalin in regions which have been deprived of their sympathetic supply. In Fig. 193 are shown the changes in surface temperature of a left finger of a subject in whom the left hand had been sympathectomized.[130] The subject received an injection of insulin which induced an increased adrenalin production. This in turn caused a marked fall of temperature in the hypersensitive denervated side. The adrenalin output was apparently quite inadequate to produce any change in the normal limb. As has already been pointed out (page 171) adrenalin may be liberated into the blood stream in concentrations adequate to produce a profound effect on the heart, and this is probably an important factor in control. In addition, adrenalin may reduce the sensitivity of the heart to acid, and this change would have an obvious significance. It is uncertain how far other endocrine glands are brought into action in the adjustments of the circulation. There is some evidence that nervous reactions may induce variations in the

secretion of the pituitary gland, and that these variations may be associated with changes in blood pressure. Stimulation of the central end of a cut vagus nerve usually causes a rise in blood pressure. Sattler[272] found that this rise in pressure could be produced in animals in which the neck had been crushed so that no nervous connection existed between the head and trunk of the animal. The rise in pressure was therefore of humoral origin. It was abolished by removal of the pituitary or by division of the tracts passing from the supra-optic nuclei to the hypophysis. This evidence, however, does not prove that these reactions are concerned in all, or even in many of the circulatory adjustments. The posterior pituitary plays a role in the control of fluid balance, and it is possible that the rise in pressure is one concerned solely with such adjustments.

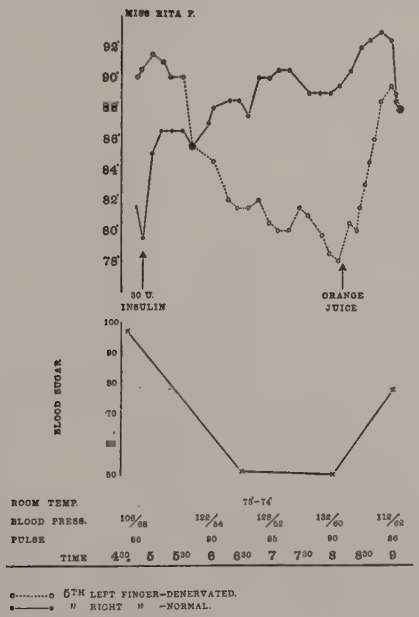


Fig. 193.—Chart showing changes in the temperature of the fingers of the right and left hands of a patient. The changes in the left sympathectomized hand (indicated by a dotted line) may be compared with those of the normal right hand (continuous line). The hypoglycemia, induced by injection of insulin (arrow) produced sympathetic activity. The adrenalin liberated caused marked constriction of the sensitized vessels of the sympathectomized finger. (From Freeman, Smithwick, and White: Am. J. Physiol. **107**: 529, 1934.)

In an animal in which the nervous mechanisms have been partially destroyed, as in a sympathectomized cat[249] or in one with the spinal cord pithed,[82] the addition of CO_2 to the inspired air produces a simple fall of pressure. Presumably this is dependent on a peripherally induced vasodilatation. In a decerebrate cat inhalation of only 3 per cent CO_2 may produce a doubling of arterial pressure.[106] Such increases in pressure are accompanied by reductions in pulse rate of only about 6 per cent. Anesthetization greatly reduces the response. A similar pressor effect of central origin may be obtained in a

decapitate cat, in which the buffer nerves can no longer act, but its elicitation requires CO_2 concentrations some ten times as great as those necessary to affect the bulbar centers.[232, 233] These experimental facts show that the medullary centers and spinal centers react to excess CO_2 by inducing vasoconstriction. In the spinal animal the pulse rate changes are small and probably depend in part on secondary effects on the coronary circulation. In the intact animal they are also small as the result of the balancing of opposing factors.

Not only does CO_2 excess produce an increase in pressure but removal of CO_2 by hyperventilation causes a profound fall. The change is due to a lowered peripheral resistance caused by a depression of the medullary and spinal vasomotor centers (Dale and Evans[82]). The pressor response to sensory stimulation is also decreased. Yet in man voluntary hyperventilation may sometimes give a rise of blood pressure and this is usually associated with marked peripheral vasoconstriction. The latter is probably dependent on the direct peripheral effects of a lowered CO_2 tension.

The effects of CO_2 are produced mainly by direct action on the medullary centers. To a lesser extent they depend on reflex effects exerted through the carotid and aortic bodies. Effects are also produced on these bodies by decreases in pH, and by O_2 lack. Possibly the effects of O_2 lack are due to acid changes. While the effects of CO_2 are largely dependent on direct central action, those of O_2 lack are almost entirely reflex and are produced through the carotid and aortic bodies. As with excess of CO_2 there is a rise in pressure and slight slowing of the pulse in the intact anesthetized animal. According to most observers these changes are slight or absent, if the nerves from these receptors have been divided. The slowing of the pulse with anoxemia so obtained experimentally is in strong contrast with the increase in pulse rate found in man on exposure to even moderately low oxygen tensions. Either the reflex responses are modified by some procedure to which the animal has been subjected, or some additional factors play a role in man. Though pure O_2 lack is described as a simple depressant to the circulation in animals deprived of the reflex effects by nerve section, this is not the whole story. Marked pressor responses to anoxemia induced by the breathing of nitrogen have been described by Matheson[232] in decapitate cats. In such animals not only have these receptors lost their central connections but also the medullary centers have been removed. Thus it is possible that spinal centers are stimulated by oxygen lack, and probable that medullary centers are stimulated by certain levels of oxygen deficiency.

The peripheral, and possibly also the central and reflex, effects of CO_2 or of lactic acid may depend on the degree of acidity reached. In estimating the local effects of acidity Atzler and Lehmann[10] find in frogs that the maximum dilatation occurs at pH values between 5.6 and 6.5. At lower values the vessels react by constriction.

A Renal Pressor Factor.—Another chemical factor of importance in disease is one apparently produced in the kidney. This is demonstrable in the production of renal hypertension. Presumably this factor also exerts an influence in the normal circulation, though nothing is known of its mode of action or normal function. This factor was first demonstrated conclusively by Goldblatt.[141] He found that interference with the flow of blood through the renal arteries produced by a mechanical clamp caused the development of a permanent hypertension. The hypertension was particularly marked if the circulation was slowed

through both kidneys. Removal of the kidneys may also cause a rise of pressure, but this is much less marked. A slow renal circulation appears to liberate into the blood stream some substance which produces general vasoconstriction. The effect is chemical, for it can develop in sympathectomized animals, as well as in animals with their spinal cords destroyed. A substance, known as *renin,* which has pressor effects may be extracted from kidney tissue. According to recent work renin is an enzyme which acts on a pseudoglobulin in the plasma to form the active pressor substance. The plasma pseudoglobulin is called the "activator" by Page, though it may be the substance on which renin acts. The active substance formed has been called *angiotonin.* Depressor substances have also been extracted from kidney, but it is not known whether either these, or the pressor substance, renin, are normal physiological products. The conditions of the circulation in the presence of hypertension will be discussed later.

The Coordinated Response.—One may conclude that the supply of blood to an active area is largely determined by the local vascular action of metabolites formed during activity and that this is assisted, particularly at the start of such activity, by reflexes which improve the local blood supply. These reflexes act also to modify the circulation in other areas so as to make available as large an amount of blood and as high a pressure head as possible. At the same time intrinsic reflexes which control the circulation as a unit come into play and prevent too great a strain being placed on any section. The activity of these intrinsic reflexes is modified not only by sensory impulses from the extrinsic systems, but also by the chemical action of metabolites which may accumulate in the arterial blood. It is impossible at the present time to specify exactly the chemical substances involved in this control. Probably CO_2, lactic acid, histamine, and possibly adenylic acid and products of the breakdown of nucleoproteins are concerned in producing the local response. Many of these substances may act also by modifying the activity of various centers. The variation in response of the vessels of different areas to any given degree of acidity and to adrenalin is probably of importance. In the muscles variations in vascular tone may be brought about through the effects of the local changes in temperature that accompany activity.

It is obvious that not only must circulatory reactions be coordinated with one another, but also with those of respiration. This coordination is probably effected largely through chemical influences, but receptor organs such as those of the carotid sinus and body influence both circulation and respiration. In addition, certain respiratory changes may modify the circulation. It has been found that vasoconstriction is induced by deep inspiration.[41] The functional importance of this change is at present unknown.

The maintenance of a normal vascular tone is probably attained not only by nervous but also by chemical means. The internal secretions of various glands may be concerned in the latter.

The various factors that may play on the cardiovascular centers and influence their tone are indicated diagrammatically in Fig. 194. The effects of these variations in tone produced by intrinsic reflexes set up by high arterial or by low venous pressure are indicated at the bottom of the figure. Fuller diagrammatic representation of the changes produced in the afferent systems have already been given (Fig. 146, page 399 and Fig. 173, page 444). The occurrence of arterial constriction as a compensatory reaction to raise a subnormal venous

pressure is likely, at first glance, to appear illogical. But constriction by reducing the capacity of the arterial system displaces blood into the veins. Flow through the arterial system is not decreased (contrast the *local* effect of a *local* constriction) by general constriction if the heart is able (through the effect of Starling's law) to eject its normal output. The constriction may also lower capillary pressure, and so increase the blood volume through passage of fluid from the tissue spaces into the blood. If fluid is absorbed and blood volume increased, the veins may become distended. Though the pressure head for the return of blood from the capillaries to the heart is reduced, the distended veins offer less resistance to flow. Venous return is therefore improved.

The various factors may balance one another somewhat irregularly. As a result there may occur slow variations in arterial blood pressure which may or may not be associated with similar fluctuations in respiratory activity. These spontaneous fluctuations are called, after their original discoverers, Traube-Hering waves. They may be seen in unanesthetized animals and in man. They

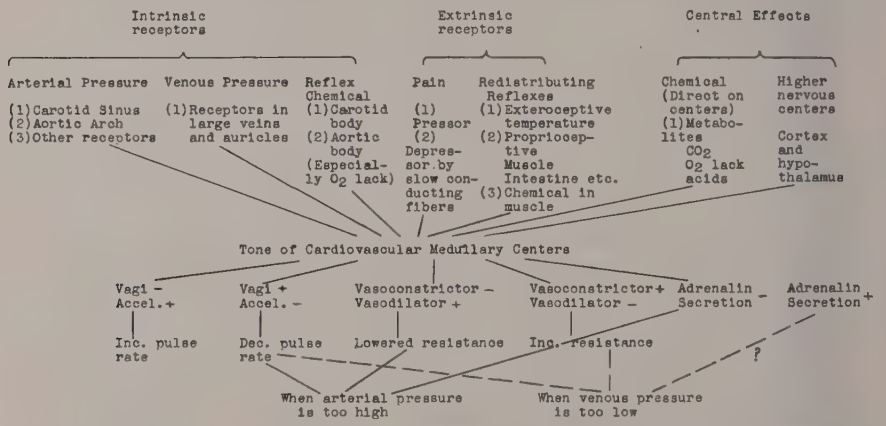


Fig. 194.—Schematic representation of the influences which affect the tone of the vasomotor centers. The reciprocal action of these centers is also indicated.

are associated with rhythmical waves of contraction of the vessels in the skin and in other areas.[320] According to Burton[60] the rhythmicity of contraction in the skin vessels varies with the thermal conditions. Thermal equilibrium is attained not by an exact setting of the degree of vasoconstriction but by a regulation of the relative durations of periods of constriction and relaxation.

EXAMPLES OF REGULATION

Modes of regulation may be indicated by a few examples described briefly in outline.

Postural Reactions.—When an individual changes from the lying to the standing position gravity reduces the pressure in the carotid sinuses and lowers the distention of the large veins near the heart since venous return is impeded. It also causes an increase in the arterial pressure in vessels in the dependent parts, such as the foot. Reflex compensatory responses include a

speeding of the pulse rate (carotid sinus) and a general vasoconstriction which may raise blood pressure if cardiac output is well maintained (carotid sinus, and reflexes from veins); slight movements of the limbs are made (unless voluntarily inhibited) and these tend to improve venous return (reflexes from veins?). There must also be variations in the degree of vasoconstriction in different parts of the body. As the result of the high arterial pressure produced by gravity much of the blood would tend to pass through the most dependent parts, such as the foot, unless the arterioles in these parts are more constricted than those in less dependent parts. However, in the absence of muscular movements venous pressure rises in the veins of the legs and can neutralize the simple mechanical effect of gravity on the flow in the arteries. The reflex mechanisms which determine distributional variations in vasomotor tone are not known. The net effects of all these changes are: a cardiac output per minute somewhat below the value in the lying position in spite of the increased pulse rate; a considerably reduced stroke volume; a mean blood pressure level which, as measured at the heart level, is usually raised and is therefore raised in relation to receptors in the aortic arch but which is often subnormal at the level of the carotid sinuses; a somewhat inadequate filling of the heart and presumably subnormally distended central veins; a lower pulse pressure which accompanies the reduced stroke volume and which implies therefore a rise in diastolic pressure exceeding the rise in either mean or systolic pressure.

There may be more or less complete compensation, if some muscular movements which aid venous return are allowed. There is then some rise in capillary pressure in the dependent parts, with increased formation of tissue fluid. As a consequence the tissue fluid pressure is raised within the fascial sheaths of the leg muscles; in the gastrocnemius the pressure may reach values of over 20 mm. Hg (Mayerson and Burch[236]). This raised pressure will then prevent further filtration of fluid in spite of the high capillary pressure. If the subject be tilted on a movable table, so that muscular movements may be effectively inhibited, such a rise in tissue fluid pressure within the muscles may not occur. When it does not take place the subject is likely to faint. Possibly the absence of movements allows pooling of blood in dependent veins, leaving inadequate fluid available to raise the pressure within the muscular sheaths. Whether movements are or are not allowed, collection of fluid in the subcutaneous tissue is not only slow but also develops without any marked change in tissue fluid pressure. Presumably local vasoconstriction leaves only small volumes of fluid available.

Reactions to Temperature.—Under warm conditions the superficial vessels have to be dilated to favor heat loss; dilatation of the superficial veins is important and for this purpose they need a considerable volume of blood. To make this blood available either the central vessels must be constricted, or the blood volume must be increased. Constriction of the central vessels forms part of the reaction to acute exposure to warmth, and constriction of large central veins probably plays a role. Constriction of centrally located arterioles (utilized for its capacity effect) may also develop and may result in an increase in arterial pressure through the concomitant increase in the effective peripheral resistance. Such a reaction is similar to one which may be seen after hemorrhage (see page 521). The individual may be regarded as having bled into his own veins. The maintenance of central vasoconstriction implies a strain with inadequate circulation in certain areas. It is not surprising, therefore,

that there is commonly also an increase in blood volume. Any acute increase is limited, for no great change in blood volume can be induced rapidly without a considerable reduction in plasma protein concentration. If a demand for an enlarged vascular bed, and consequently for an increased blood volume, is long maintained, mechanisms may be set in motion which increase the quantity of the plasma protein and allow the change in blood volume to be larger. Central vasoconstriction may then be relaxed. The reflexes involved in the production of this series of changes are uncertain. Probably the superficial vasodilatation is dependent on exteroceptive impulses from thermal receptors. The superficial dilatation in its turn would produce secondary adjustments through intrinsic reflexes set up by proprioceptive receptors in the vascular bed. Here inadequate filling of large central veins may play a part as well as variations in the frequency of impulses resulting from changes in the distention of the carotid sinus and aortic arch. Effects are no doubt produced by changes in temperature on the carotid and aortic bodies, but they have as yet not been adequately analyzed.

Dilated superficial veins make the return of blood to the heart in the standing posture more difficult, and the increase in pulse rate and reduction in stroke volume that occur in the standing posture are exaggerated. The mean blood pressure may fall. When a subject has become adapted to the higher temperature, the circulatory changes on standing may be subnormal rather than exaggerated. The changed reaction appears to be associated with an increased blood volume, so that pooling of blood in the limbs has less effect.

Reactions to Exercise.—The circulatory changes with muscular exercise are described later (see page 855). They may be seen to fit into the general picture of regulation by intrinsic reflexes in a circulation with a large venous return maintained by a muscular pump. There may be considerable increases in arterial pressure; in the figures cited on page 858 there was an increase in mean pressure of 40 mm. or more, and in systolic pressure of 60 mm.; yet the pulse rate was 150. Even higher pressures, associated with still higher pulse rates, may be recorded. Reflexes from the carotid sinuses initiated by the high pressures may be operating to slow the heart, but they must be very ineffective. Presumably they are counteracted by other reflexes initiated from the large veins, carotid and aortic bodies, and other receptors including those within the muscles, which maintain the high pulse rate. Both this high pulse rate and the raised arterial pressure are essential if a really high rate of flow is to be maintained in the arteries.

Reactions Under Abnormal Conditions

Inflammation and Fever.—In inflamed areas there is a local dilatation which is brought about mainly through an axon reflex. It can develop in an area completely insensitive to pain and in one in which sympathetic vasoconstriction is not modified reflexly. Thus it was originally demonstrated by Bruce[53] in the conjunctiva when section of the Vth nerve, central to the Gasserian ganglion, had destroyed all sensation and all responses of a true reflex nature. If the Vth nerve was divided peripherally to the ganglion, the reaction disappeared when the nerves began to degenerate. Such inflammatory reactions are assisted by reflexly produced relaxation of vasoconstrictor tone in the area. The blood flow may also be accelerated by a rise in blood pressure

produced reflexly by changes in cardiac output and pulse rate, as well as by increased vasoconstrictor activity in the rest of the body. Consequently, the arterial blood pressure is raised in the reaction of a normal individual to a severe inflammation, such as that accompanying a compound fracture. In young subjects systolic pressures exceeding 150 mm. Hg are common under such conditions. The raised blood pressure accompanies the period of acute inflammation and high fever. Only if the individual is too ill to react adequately is the pressure rise absent.

Fever associated with widespread inflammation may, on the other hand, be accompanied by a lowered blood pressure. Thus typhoid fever with inflamed areas scattered widely over the splanchnic area is likely to induce a low pressure. The marked reduction of the effective peripheral resistance likely to result from such widespread inflammatory changes may be the cause of this. Areas capable of compensatory vasoconstriction are probably too limited.

Vasomotor adjustments associated with temperature control may play a part during the rise and fall of temperature in fever, for during a rapid rise in temperature there is skin pallor and probably contraction of the arterioles; the superficial veins are also constricted. As soon as the peak of the fever has been reached, and the temperature is falling, cutaneous vasodilatation with relaxation of the superficial veins is seen. Consequently, in the chill of malaria the blood pressure is raised, and during the fall of temperature it is lowered.

Peripheral Vascular Disease.—The circulation in the peripheral vessels may be impeded by abnormally intense contraction of the circular muscles, or by structural changes in the vessels which reduce their lumen. The former is amenable to relaxation by sufficiently strong reflex changes; the latter is due to a structural change (e.g. fibrosis), which no muscular relaxation can remove. Estimates of the rate of blood flow under conditions in which vascular relaxation prevails may therefore be utilized for clinical differential diagnosis. One method of obtaining such relaxation is by producing a reflex dilatation with heat; another is by paralysis of the vasomotor nerves by local anesthesia of a nerve trunk. The presence or absence of a fast blood flow may be determined by the capacity of the blood stream to raise the surface temperature in a limb previously cooled. If a fast blood flow cannot be induced, the presence in the vessel walls of organic changes which seriously restrict the lumen may be assumed. It must be remembered that in the normal subject relaxation of vessels can modify resistance to flow and that consequently a rise in blood viscosity due to an increased red cell concentration is of little consequence. However, in subjects in which relaxation of vessels cannot occur, any such increase in viscosity may impose a serious strain.

A method in common use for testing the reflex effect of heat in raising surface temperature by vasodilatation is that developed by Gibbon and Landis.[136] These workers use a low room temperature (15° to 17° C.) and allow the exposed limb to cool; if the legs are under investigation the hands and forearms are plunged into hot water at 45° C., and after five or ten minutes a marked hyperemia may be seen all over the body, and the skin temperature of the limb under investigation is raised. If the circulation is normal the skin temperature, even of the toes, is raised to about 33° or 34° C. (Fig. 195). If the circulation is subnormal and cannot be increased by vascular relaxation, the temperature rise falls far short of this level (Fig. 196). When an adequate rise in temperature fails to occur, it indicates organic disease rather than spasm. This may be confirmed by the use of spinal or nerve trunk anesthesia, with the determination again of the degree of rise of surface

temperature. If a rise in temperature still fails to occur, nervous vasoconstriction can be completely excluded as a causative factor. The methods are, with slight modifications, applicable to the investigation of the forearms and hands.

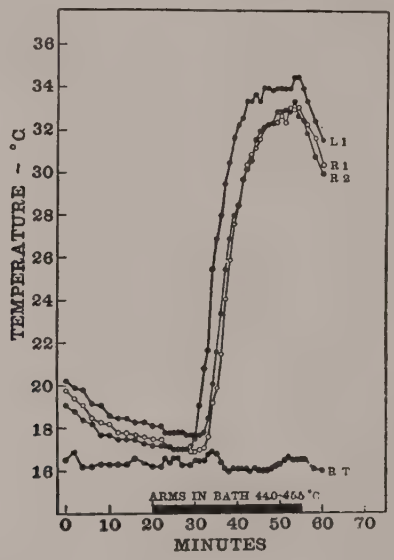


Fig. 195.—Rise in temperature in right (R_1 and R_2) and left (L_1) toes when forearms and hands are immersed in hot water. Normal subject. R. T. indicates room temperature. (From Gibbon and Landis: J. Clin. Investigation 11: 1019, 1932.)

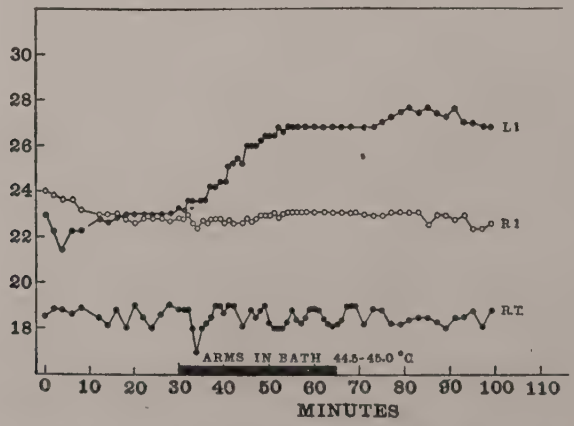


Fig. 196.—Record of an experiment similar to that of Fig. 195, but carried out on a subject with arteriosclerotic obstruction of blood flow to the legs. The pathological condition was more pronounced in the right leg. (From Gibbon and Landis: J. Clin. Investigation 11: 1019, 1932.)

Local Circulatory Defects Entirely Due to Spasm.—These include those of the Raynaud type and the related conditions of acrocyanosis and scleroderma. In these a spasm of contraction is brought on usually by cold, possibly by emotional disturbances. Any intense

vasoconstriction will allow local cooling of the tissues, and cold may therefore be a precipitating cause, even when it is not the primary initiating factor. In such cases crossed reflex vasoconstriction to cold applied to other limbs is exaggerated.[291] In these individuals spasms of vasoconstriction, particularly involving the fingers and toes, occur and cause local cyanosis and pallor. The attacks are extremely painful and the local anemia may give rise to gangrene. The vessels affected are, according to Lewis and Landis,[218] primarily the digital arteries and arterioles; capillary contraction is considered to develop secondarily after stasis is established. Removal of the sympathetic supply of the extremity separates the vessels from central vasoconstrictor control, and a vasodilatation with rise in temperature of the part results from interruption of the tonic vasoconstrictor discharge. In the case of the lower extremities it is easy to section the preganglionic fibers (by cutting the lumbar chain) and to leave intact the postganglionic neurons. It is, however, almost impossible to effect a simple section of the preganglionic portions of the sympathetic pathway to the upper extremities. In this case the surgeon must perform the operation of ganglionectomy which results in degeneration of postganglionic fibers. It will be recalled (see page 474) that denervation of sympathetically innervated effectors results in sensitization to adrenalin and sympathin and that this sensitization is much more pronounced when the postganglionic fibers are interrupted. This probably accounts for the fact that the surgical treatment of vascular spasm has given far better results in the foot than in the hand. When the denervated smooth muscle has become hypersensitive to adrenalin[91] (and perhaps to other chemical agents) vascular spasm, no longer possible from nervous activity, may result from chemical changes.

Hypertension.—A condition of hypertension in which the mean arterial pressure is raised can result from only two causes, namely, increased cardiac output and increased peripheral resistance. The former can be discounted as a common cause of clinical hypertension, for measurements show that cardiac output is normal or subnormal. Only when metabolism is increased, as in certain cases of hyperthyroid disease, is hypertension associated with a rapid pulse and increased cardiac output, but the ordinary case of hyperthyroidism shows only a moderately raised systolic pressure which, like that of exercise, is determined by increased cardiac output overbalancing lowered peripheral resistance. The toxic form of this condition may occasionally be exaggerated into one of still higher tension with a fast pulse rate.[116] Increased peripheral resistance may be taken, therefore, as the usual cause of hypertension. The types may be differentiated into those with no demonstrable renal involvement (called essential hypertension), those with renal involvement, and those in which the normal changes of age may be considered the main factor.

Renal hypertension may be produced experimentally by interfering with the renal circulation. Mean blood pressure is raised by increased resistance; pulse pressure is also increased, for the systolic change exceeds the diastolic. The increased pulse pressure is probably due to decreased distensibility secondary to the pressure change and dependent on the greater part played by the less distensible adventitious coats of the vessels at the higher pressures. The increased resistance is due, at least in part, to a widespread arteriolar change. This involves the vessels in the arm, for the flow there is found to be normal or subnormal in spite of the high pressure head.[250] The increased resistance in the arm vessels must be exaggerated by arteriolar contraction, for it may be reduced if the arm is warmed, the nerves paralyzed by novocain, or if reactive hyperemia be induced by a previous stasis. Yet even when the vessels are dilated by one of these procedures they give evidence of some constriction, for in spite of the high pressure the rate of blood flow is not increased above the limits seen in normal persons. For instance, normal subjects with the arm immersed in water at 45° showed flows averaging 14.9 ml. per 100 ml. of arm per minute, while hypertensives of the nephritic type had flows of 14.0 ml. Two groups of individuals suffering from the two types of essential hypertension (benign and malignant) had flows of 15.0 and 14.6 ml., respectively.[250] The small differences between these figures show that the hypertensive individual has a high effective peripheral resistance. Were this not the case their high pressures would induce supernormal flows. The approximate mean pressures of the 4 groups were, respectively, 90, 148, 169, and 191 mm. Hg; the effective resistance in the arms of the abnormal subjects was increased 50 to 100 per cent. Superimposed on this increased resistance there is a vasomotor control capable of adjusting the blood flow in accord with local conditions.

Owing to this vasomotor control, changes in blood pressure may be produced as in a normal subject by carotid sinus stimulation, and the peripheral vessels can probably be

affected reflexly not only by the temperature changes already described but also by other stimuli. An extensive literature is being built up on the study of both clinical and experimental renal hypertension. A useful summary is given by Blalock.[40] The subject will not be discussed further here; suffice it to say that an understanding of renin and its action on the circulation might give the key to a better understanding of the relationships of humoral agents to the circulation and fluid balance. The chapter on the integrative action of these agents in physiology has yet to be written.

Essential hypertension may also be of renal origin and depend on some interference with blood flow through the kidney, even though gross renal lesions are not in evidence. The clinical picture has resemblances to that of renal hypertension (see page 476). Reactions to carotid sinus stimulation are normal.[133] The condition may be relatively "benign" or "malignant;" in the latter case the condition progresses rapidly. The physiological

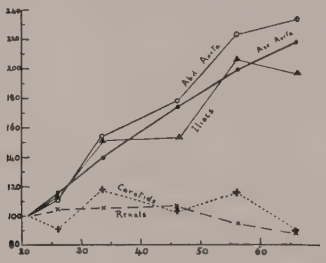


Fig. 197.—The percentage increase in the cross-sectional areas of various vessels (ordinates) plotted against age in years (abscissae). (Data from Kani.[38])

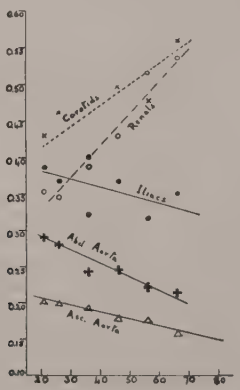


Fig. 198.—Ratio of thickness of the vessel wall to the internal radius plotted (as ordinates) against age in years (as abscissae). (Data from Kani.[38])

causation of such rapid changes is unknown. Arteriosclerotic changes develop in the vessels with thickening of the walls of the smaller arteries.[201] These appear to be results, rather than causes, of the hypertension, though, once established, they no doubt cause a considerable increase in resistance. Extrarenal causes are a possibility, if not a probability, in at least some cases of essential hypertension. Possible causations of hypertension are: (1) interference with the circulation to centers in the medulla as the result of local vascular disease, in which case the reaction would then be akin to that produced in the centers by asphyxiation (see Raab[251]), and (2) it could (from an experimental viewpoint) be dependent on failure of the buffer nerve mechanisms (carotid sinus and aortic arch). It seems certain that the second of these hypotheses can be excluded in nearly all clinical

cases. The carotid sinus reflexes appear normal. Lasting hypertension can be produced in animals by section of these buffer nerves, but it is associated with a rapid pulse. In clinical hypertension the pulse is usually slow.

Age Changes and Hypertension.—With the attainment of adult life arteriosclerotic changes commence in the vessels and develop more rapidly in those exposed to hypertension. In the larger vessels there is an increase in the lumen, in the smaller vessels a decrease (Figs. 197 and 198). The effects of the changes in size and distensibility have already been discussed (page 406). The decreased distensibility tends to increase pulse pressure by raising systolic and lowering diastolic pressure. The thickening of the walls of the smaller vessels and the decrease in their lumen causes some increase in resistance; this tends to increase both systolic and diastolic pressures. The net effect is a marked rise in systolic, accompanied by a diastolic pressure that is often not far from normal.

CHAPTER XXXIV

LYMPH

The Lymphatic Vessels and the Pressures Within Them.—There is now general agreement that the lymphatic system consists of a branched arrangement of closed vessels not in open communication with the fluid in the tissue spaces. The lymphatics are lined by endothelium and "the lymphatic capillaries have the same relation to tissue spaces as have blood capillaries."[269] They are found in nearly all tissues, and Drinker and Field[96] consider them to be almost as numerous as blood capillaries and to have a surface available for absorption which is as great as, or greater than, that of the blood capillaries. The lymphatic capillaries collect into numerous larger channels which eventually join the lymphatic glands where they form a marginal sinus, to branch later into a rich plexus of small vessels within the gland, from which the lymph emerges by an efferent vessel. The lymph may pass through more than one gland on its way to join the large thoracic duct or one of the smaller collecting ducts, by which it is eventually carried to the large veins. The larger lymph vessels have both elastic and muscular coats. The lymphatics are richly supplied throughout with valves which allow flow only in a centripetal direction. Some of the lymphatic glands differ from the others in containing numerous red blood corpuscles; these are the hemolymph glands. Like the spleen they appear to be concerned with blood destruction. It is said that they have direct connections with blood vessels. Some doubt exists whether they are actually connected with the lymphatic system proper.[243]

The pressure in the peripheral lymphatics is low. They may be occluded by pressures of only 1.5 to 3 mm. Hg. In the larger more central trunks the pressures appear to be as low as 0.5 mm. or less. Drinker and Field cannulated a lymphatic in the popliteal space in a dog in such a way as not to obstruct the flow, and were unable to record any positive pressure or flow when the limb was at rest. Massage, however, not only created flow but raised the pressure to 50 mm. Hg. When lymph flow is increased in this way the lymph nodes, through which the lymph flows, swell and offer increasing resistance to its passage. There can be little doubt that the pressure in lymphatics is low when the area they drain is at rest, and that the flow is also low—possibly zero. When passive movements, and probably still more when active movements, are made, flow of lymph is started and relatively high pressures may be developed, particularly if the flow is in any way impeded. Possibly the normal resistance of the lymph glands to rapid flow may create such an obstruction. Under conditions of sterile inflammation in the foot Drinker and his associates have observed pressures as high as 88 mm. Hg in the lymphatics at the ankle. The pressure in the thoracic duct, like that in the large thoracic veins, is affected by the subatmospheric intrathoracic pressure, and is normally maintained slightly subatmospheric with exaggeration during forced inspiration. There can be, therefore, a considerable pressure gradient favoring flow of lymph, but only under certain circumstances.

The Flow of Lymph.—The amount of lymph flowing in a peripheral area, such as a limb, is extremely variable, and depends, as has been mentioned, on the activity, and particularly on the movement, of the part. The Clarks[71] have studied lymphatics in the ears of rabbits. They were able to identify within these lymphatics cells which, though apparently free in the lumen, did not move consistently in any direction over long periods of time. The lymph in such cases appears to be stagnant and to have no consistent movement. On the other hand, Drinker and Field[96] report that trypan blue injected in the foot of a dog may enter a lymphatic, and, if 2 or 3 ml. be injected, this fluid may reach the thoracic duct within half a minute or less. The volume of lymph produced in the foot of a dog during walking was found to be of the order of 0.1 to 0.7 ml. per minute. A drainage of about 1.5 ml. per minute has been reported from a lymphatic fistula in the thigh of a man. Lymph flow, like the pressure within the vessels, appears, therefore to be quite variable and normally not very great in volume even during activity.

The Composition of Lymph.—The protein concentration of lymph varies considerably. The lymph from cervical and limb lymphatics has a protein concentration of some 2.3 per cent, that from the thoracic duct about 3.2 per cent, but lymph collected from a limb during exercise may contain less than 0.5 per cent protein. If the inferior vena cava be partially obstructed, and the pressure in the hepatic veins be thus raised, there is usually obtained from the liver a marked flow of lymph which may contain almost as much protein as does the blood plasma.[286] Thus the protein concentration of lymph from different areas varies. A similar variation is found in the lymph from a single area; in the latter case the variations depend on the rapidity of lymph flow and on the conditions generating this flow. The lymph from the thoracic duct contains fibrinogen; when shed it slowly clots. It also contains serum albumin and serum globulin. The colloid osmotic pressure of lymph depends on these proteins, and on the relation of the concentrations of the various proteins to one another. Direct measurement of samples which contained 1.7 per cent or more protein gave values between 4 and 20 mm. Hg.

The concentrations of salts and other diffusible substances appear to be close to those found in plasma; that of calcium is somewhat lower, that of chlorides and of nonelectrolytes is somewhat higher. The thoracic duct lymph contains large numbers of white cells, which are almost entirely lymphocytes. The numbers observed vary greatly, from 500 to 72,000 per c.mm.

Relations of Blood Plasma, Tissue Fluid, and Lymph to One Another.—The description of the lymphatics given above has followed closely that given by Drinker and Field,[96] who emphasize not only the variable protein content of lymph, but also the fact that this can be relatively high and so exert a very definite colloid osmotic pressure. They also present evidence that there is normally little flow without movement, and that movement is the main factor in creating such flow. Throughout the discussion of the circulation emphasis has been placed on the colloid osmotic pressure of the blood, on the filtration of fluid from blood at the higher hydrostatic pressure that exists at the arteriolar end of a capillary, and on the absorption of this fluid at the venous end where the hydrostatic is below the osmotic pressure. The relation of the tissue fluid thus formed to lymph must now be considered. The subject is a controversial one, of which only one side will be presented.

Under conditions of normal flow in a blood capillary, tissue fluid is formed and reabsorbed in the way described. Because of the relative impermeability of the capillary wall to large molecules this fluid contains very little protein. Probably the tissue fluids contain not more than 0.3 per cent of protein. The amount is about the same as that found in normal cerebrospinal fluid, which it is perhaps correct to regard as a specialized tissue fluid. On these assumptions the colloid osmotic pressure of the tissue fluid would amount to about 1 mm. Hg. Consequently the difference between the effective osmotic pressure of the blood in the capillaries and that of the tissue fluid would be about 25 mm. Hg. It is possible that the small amount of colloid present consists of the smallest protein molecules, and might be able to repenetrate the blood capillaries at the venous end. Even under normal physiological conditions, the capillaries are probably not continually in a "healthy" state. A very short period of anoxemia renders the capillary wall highly permeable to protein (see page 449), but it readily regains its permeability on the restoration of a normal oxygen supply. Anoxia of some degree must be a common occurrence in many capillaries. Such must be the condition of many of the capillaries in the reader's buttocks as he sits and reads these words. For a short time after release of the compression and re-entry of blood, these capillaries would in all probability be highly permeable to protein. On further recovery of the capillary wall this protein will be unable to re-enter the blood and it will, therefore, exert an osmotic pressure in opposition to that of the plasma proteins within the vessels. One may assume that reabsorption of fluid occurs in the small venules where the blood has a pressure of only about 11 mm. Hg, and there is consequently an osmotic force of some 15 mm. acting to absorb fluid into these vessels. If the tissue fluid has a colloid osmotic pressure less than this (with a protein concentration of less than 4 per cent), water and salts can be reabsorbed until the colloid osmotic pressure of the tissue fluid is so increased that a balance is attained between osmosis and filtration. The presence of protein in the tissue fluid also would tend to increase the separation of fluid from the blood at the arteriolar ends of the capillaries, for the retaining effect of the colloid osmotic pressure of the blood would be reduced.

In the absence of lymphatics the condition just described might be permanent; actually within a short period normal fluid balance is re-established with no indication of protein in the tissue fluid.[208, 210] There is much evidence to indicate that the lymphatic capillaries are very permeable, and that they will allow even visible particles to pass into them without much difficulty. Under the influence of an increased rate of fluid transudation even a relatively protein-rich tissue fluid would tend to pass into these vessels. Once it is within the lymphatics it can move only in one direction because of the valves, and any pressure from without, however produced, would force it on into vessels with thicker and less permeable walls. One source of pressure is probably the pulsations of the arteries. This concentrated tissue fluid, containing protein and enclosed in a system of vessels in which fluid transference by osmosis is no longer easy, is what is called lymph. It is moved on slowly under low pressure by every slight movement, and rapidly under the much higher pressures set up by active movements. On the basis of the foregoing exposition the formation, composition, and flow of lymph offer few difficulties except in the matter of transport from tissue fluid to lymphatic capillary.

Though the lymphatic system appears to consist of closed vessels, tissue fluid containing any protein that is present can penetrate it readily. It is also certain that large inert particles can also penetrate the vessels. The simplest hypothesis is that the cells lining the lymphatics can transport such particles by a process of phagocytosis. But this theory appears inadequate to explain the rapidity of transport. Particles introduced into the peritoneal cavity may be found in lymphatics in the diaphragm within five minutes. Florey finds that carbon particles introduced into the thigh of a rat appear in the lymph glands at the bifurcation of the aorta within twenty minutes, provided that the thigh muscles are tetanized at intervals. If the thigh be kept at rest there is scarcely any evidence of such transport even after twenty-four hours. Movements may have much to do not only with the flow of lymph but also with entrance of substances into the vessels.

The observations of Allen and Vogt[7] make our understanding of the permeability of the lymphatic vessels clearer. They found that the massaging effects of movements, even of excised tissue, causes particulate matter to enter the lymphatic vessels. Drinker and Field noted that lymphatics tend to run in fibrous planes as though fibrous tissue support is necessary to them. One may suppose that movements of vessels supported in this way create suction pressures within them, and that their walls become discontinuous when stretched still further. Particulate or other matter in their neighborhood would then be sucked into the lymphatic vessels. As the continuity of the wall is restored by the release of the stretch, such matter would be retained. Massage effects produced by movement would then be of immense importance. The therapeutic effects produced by passive massage may similarly be largely dependent on such factors. Lymphatics from the intestines arise in loops within the villi. It is not improbable that contractions of the smooth muscle of the villi may have much to do not only with the movement, but also with the formation, of intestinal lymph.[124]

The lymphatics doubtless aid in the maintenance of tissue nutrition. For example, the passage of protein from tissue fluid to lymph after a period of tissue anoxia probably aids in the transudation of fluid from the blood capillaries. It should again be emphasized that anoxia is not an uncommon condition in certain tissues. When muscles contract vigorously their oxygen requirement exceeds their oxygen supply, and they continue to respond anaerobically (see Chapter LII). Although mechanical factors contribute to the greater flow of lymph from a region of muscular activity, an increase in permeability of the blood capillaries must play an important part in its production. Indeed such a change in permeability seems to be an invariable accompaniment of activity; it is a result which may be due to anoxia, accumulation of metabolites, or the production of specific substances, such as histamine.[11, 12] However caused, it apparently leads to an increased lymphatic drainage which would beneficially supplement the exchange of material between the blood and the active tissue cells. It is perhaps possible that in the activity of glands or muscles substances are produced which do not readily diffuse through the blood capillary wall. By osmotic effects they would increase the passage of fluid from the arteriolar end of the capillary and decrease the reabsorption of fluid at the venous end. If it happened that the lymphatic capillaries were more permeable to these substances than the blood capillaries, they would of course gain access to the blood by the lymphatic detour. Such a process would promote the exchange be-

tween tissues and blood. In the case of mechanical, thermal, or bacterial injuries one has only to invoke the histamine theory, so popular at the moment, to account for a flow of lymph of relatively high protein concentration. Bacteria, tissue débris, or foreign bodies which gain access to the lymph attract phagocytic cells as they pass through the lymph glands and are in this way disposed of.

Drinker and Field report that when the flow of lymph from an active area (e.g., from the foot in walking or running) becomes constant the lymph protein also becomes constant between 0.5 and 1.5 per cent. They ask this pertinent question: "Does this amount of protein represent the concentration in the filtrate from the capillaries, or has absorption of water by capillaries been a constant factor in the situation, so that the tissue fluid which we collect as lymph has a higher protein concentration than the capillary filtrate?" They point out that this "is a question which cannot be answered with finality." It is, however, a very fundamental one which further work may clarify. In this connection an experiment carried out by these investigators is so instructive that it merits brief mention. After a dog had run for four minutes, the protein content of the lymph from its foot was 1.42 per cent. The animal was then fed and allowed to rest for sixty-seven minutes. At the end of this time lymph obtained by massaging the foot contained 2.12 per cent of protein. They conclude that "Quiescence with lowered capillary pressure, and the need for water during digestion, have caused active reabsorption."

Analyses of pericardial and peritoneal fluids have been reported by Maurer and others[235] from Drinker's laboratory. They find the chloride concentrations somewhat higher than those in the blood, and the differences are of an order that can be predicted on the basis of a Donnan equilibrium. They consider these fluids to be ultrafiltrates from the blood. The protein concentration of such fluids is by no means negligible; it averages in dogs 1.7 per cent, with a minimal value of 0.83 per cent. The average value is of the order of about one-fourth that of the proteins in serum. These workers consider that such fluid represents normal tissue fluid. According to the view here presented it would present normal tissue fluid mixed with other tissue fluid formed in areas in which the capillary permeability to proteins was temporarily abnormally high.

The importance of muscular activity in lymph formation makes recent observations on lymph production in the heart (Drinker et al.[97]) of special interest. It has been shown that the lymphatics of the heart join to form a single vessel which runs close to the pulmonary artery. The total lymph from the constantly active heart can therefore be collected. In the dog the formation of cardiac lymph is continuous but small in amount; it averages about 0.1 mg. per gram of heart per minute. This is an amount equivalent to about 1/10,000 to 1/5,000 of the blood flow. The rate of lymph formation is increased when the work of the heart is greater, but the maximum rate of formation found did not exceed 4 or 5 times this average "resting" value. The lymph obtained from the heart contains a considerable amount of protein (average 3.69 per cent). Consequently Drinker concludes "that capillaries practically universally leak protein; that this protein does not re-enter the blood vessels unless delivered by the lymphatic system; that the filtrate from the blood capillaries to the tissue spaces contains water, salts and sugar in the concentrations found in blood, together with serum globulin, serum albumin and fibrinogen in

low concentration, lower probably than that of the tissue fluid or lymph; that water and salts are reabsorbed by the blood vessels and the protein enters the lymphatics together with water and salts in the concentration existing in the tissue fluid at the moment of lymphatic entrance. The lymph from any drainage area contains a varying amount of protein dependent upon the amount of water absorption which has taken place in the region from which the collection is made, and represents a cross-section of the tissue fluid of the area in question."

The view expressed by Drinker would at first sight appear to be directly contradictory to that given here. In reality the differences are minor. Drinker visualizes capillaries which are everywhere slightly permeable to protein; these small quantities of protein are concentrated in the tissue spaces by fluid absorption into the vessels. The opposing view is that the capillaries are for the most part completely impermeable to protein molecules, but that in any large population of capillaries a few are temporarily highly permeable. This increased permeability may be brought about by damage within the physiological range or by metabolites having a direct action of this sort and assisting in the adaptation of the individual to activity. However the protein leakage is attained, there is little disagreement on the later course of events.

The Serous Cavities.—The peritoneal, pleural, pericardial and joint cavities contain small amounts of tissue fluid, which may be increased in conditions of inflammation or of disordered fluid balance, but they are not directly connected with the lymphatic system. The drainage from the peritoneal cavity is rapid, particularly so on the under-surface of the diaphragm. This again suggests the importance of movements in relation to absorption. Cardiac movements, however, appear ineffective in speeding absorption from the pericardial sac. Here absorption is slow.

Lymphagogues.—Several types of lymphagogues have been described.[286] They probably increase lymph formation primarily in the intestine and liver, though to a less extent in other areas. The simplest of these lymphagogues are hypertonic solutions of salt or glucose. When injected intravenously they attract water from the tissues and from the fluid lying dormant within the gut by virtue of their osmotic activity. Increased fluid in the circulatory system, however, raises the blood volume, lowers the colloid osmotic pressure of the plasma, and tends to raise the effective filtration pressure in the capillaries. The initial period of fluid absorption is, therefore, followed by a second period of increased fluid transudation, which is reflected in increased lymph formation. The action of other lymphagogues, such as Witte's peptone, leech extract, and the like, depends on a toxic action which renders the capillaries more permeable to protein. The resulting lymph contains unusually large amounts of protein. In this case the flow depends on the reduction of the *effective* colloid osmotic pressure of the blood.

CHAPTER XXXV

THE PULMONARY CIRCULATION AND THE RESPIRATORY VARIATIONS IN BLOOD PRESSURE

THE PULMONARY CIRCULATION

Since all the blood returned to the heart has to pass through the pulmonary circulation, the outputs of the two ventricles must be equal except during very brief periods of adjustment. The mean pressure in the pulmonary artery, like that in the aorta, is determined by the relation of this output to the resistance of the pulmonary system. Likewise the pulse pressure depends on the distensibility of the short pulmonary artery, which acts as an elastic reservoir.

The Pressures in the Pulmonary Vessels

The Pulmonary Arterial Pressure.—The pressures developed in the right ventricle and pulmonary artery are quite low compared with those in the left ventricle and aorta. This fact implies that the effective peripheral resistance of the pulmonary system is also low. In the dog the mean pressure in the pulmonary artery is of the order of 20 mm. of Hg or less, or about one-fourth that in the systemic arterial tree. With pressures as low as this, the pressure difference between the external atmosphere and the thoracic cavity is not negligible;* the pressures developed in the pulmonary vessels must be compared with both standards. The air that is taken into the alveoli is practically at atmospheric pressure and it is this pressure to which the capillaries in the alveoli are exposed. The pressures will, therefore, be considered first in relation to atmospheric pressure; the effects of the subatmospheric thoracic level will be discussed later. All pressures mentioned will be those found with the chest closed, even though they are expressed with reference to extrathoracic pressures. When the chest is open conditions are abnormal.

Although the mean pressure in the pulmonary artery is low, the curves representing the time relations of the pressure changes, both in the right ventricle and in the pulmonary artery, are quite similar to those recorded from the left ventricle and aorta. There is, therefore, no need to reproduce examples; the left ventricular curves may simply be transposed to a different scale. The pressures determined for the pulmonary artery in the intact chest by different observers vary considerably. Recently measurements have been made in unanesthetized dogs (Hamilton et al.;[160] Katz and Steinitz[197]) which also disagree. The average values found are 37/10 and 27/11 respectively, and individual values vary from 25 to 45 for systolic, from 7 to 15 for diastolic, and from 10 to 33 for pulse pressure. The variations probably depend, as Katz and Steinitz have stated, on the degree to which the dogs were trained to lie quietly without excitement. The data suggest therefore that there are considerable variations in the pressure levels of the system even under nominal resting conditions.

*For a discussion of the cause of the subatmospheric pressure within the thorax the reader should turn to page 542.

We may assume true basal pressures of the order of 27/11 with a mean pressure of about 18 to 20 mm. Hg, but it appears that even slight activity or excitement may cause considerable alterations. The pressures stated are relative to the atmospheric pressure; the pressures developed by the right heart relative to the subatmospheric intrathoracic pressure must exceed these values by some 5 to 10 mm. Hg. Such values have actually been recorded by Hamilton et al.[160] by the use of a differential manometer.

The different forms of energy available for movement of blood are present in very different proportions from those found in the systemic circulation. The diameter of the pulmonary artery is approximately the same as that of the aorta and therefore the velocities of blood flow in the two vessels must be similar. The absolute values of the kinetic energy developed in the two vessels must be almost identical. Owing to the low pressures developed in the pulmonary system, this kinetic energy forms a much larger, and quite important, proportion of the total energy developed by the right ventricle. The pulmonary system is also remarkable for the enormous fluctuations in pressure that result from a large pulse pressure in a low pressure system. Though the resistance in the pulmonary vessels is low, these rapid variations in both pressure and kinetic energy would tend to give a pulsatile flow even in the lung capillaries, unless the short connecting vessels were very distensible.

Nothing is known as to the actual pressures existing in the pulmonary system in man. In the following discussion pressures for man are assumed to be comparable to those in the dog. They probably have somewhat higher average values, since gravity effects which must be overcome in different areas of the lung are greater.

Arterial Distensibility.—As will be seen later the flow in the pulmonary capillaries is usually steady and free from visible pulsations. This means that there must exist between these vessels and the right ventricle an adequate peripheral resistance combined with an elastic reservoir sufficient to cause the pulsations to be extinguished. It is somewhat surprising that the pulmonary artery, of no greater diameter than the aorta and much shorter in length, should be able to accommodate such a large cardiac output without larger pressure changes; its distensibility must be great.

Hochrein[176] studied the distensibility of the pulmonary artery and compared it with that of the aorta from the same individual. Although the studies were on excised, possibly abnormal, vessels, the values he obtained help to explain the situation.

Data from one of his experiments are plotted in Fig. 199. The pressures for both aorta and pulmonary artery are estimated in relation to an assumed average intrathoracic pressure level. At diastolic pressures of 69 and 19 mm. Hg, respectively, the two vessels would have the same cross-sectional area, namely, one of 1.47 sq. cm. An increase in pressure of 38 mm. in the aorta, which is equivalent to a normal pulse pressure, would increase this area to 1.54 sq. cm., an increase of 0.07 sq. cm., while a pulse pressure of 34 mm. Hg in the pulmonary artery would increase the area in that vessel to 2.82 sq. cm., an increase of 1.35 sq. cm. The pulmonary artery is obviously highly distensible at the pressures that normally obtain within it; this explains its high capacity for storing blood. According to Hochrein the walls of the two vessels are similar except for differences in thickness. He calculates that with pressures of 150 mm. in the aorta and of 50 mm. in the pulmonary artery the tension per unit cross-sectional area of wall would be the same in the two vessels. In this way he explains the similar characters of the pulmonary and aortic elements of the second sound.

Pulmonary Venous Pressure.—Only recently have measurements of these pressures been made under the conditions of a closed chest in unanesthetized

dogs (Hamilton et al.[160]). The pulmonary venous pressure is apparently affected by the same factors which operate in the case of the large systemic veins, and pulsations with characteristics resembling those of the jugular pulse may be recorded. The venous pressure averages 3 to 12 mm. Hg relative to the atmosphere, or 11 to 19 mm. relative to the intrathoracic pressure. The relation of venous to arterial pressure has also been measured directly by the same workers by means of a differential manometer. The difference varies during a single cycle from a maximum of 30 mm. to a minimum of 1 mm. Hg. These values represent the pressure gradient forcing blood through the pulmonary system under conditions of partial rest. They indicate that the distending pressure of the left auricle is 11 to 19 mm. Hg, but probably with real rest it would be lower, approximating the 3 or 4 mm. that may be found in anesthetized dogs with an open chest.

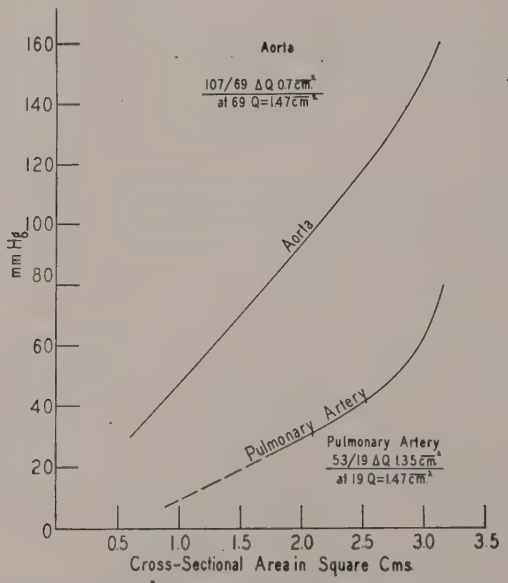


Fig. 199.—Variations in cross-sectional area of aorta and pulmonary artery (from the same animal) at different pressures. Changes in cross-sectional area for normal pressure changes are indicated (△Q), as well as cross-sectional area at probable diastolic pressures (Q). (Curves plotted from data obtained by Hochrein: Deutsch. Arch. f. klin. Med. **155**: 104, 1927. The pressures considered to exist in the pulmonary system are somewhat higher than those suggested by the more recent data that have been cited in the text.)

Pressures in the Pulmonary Capillaries.—The pressures in the capillaries of the lung are not known, even for animals. One must assume that they are below the normal diastolic arterial pressure of 11 mm. and above the normal venous pressure of about 7 mm. When the diastolic pressure in the pulmonary artery is itself 7 mm., the capillary pressure must be still lower. The pulmonary capillary pressure may be provisionally considered as about 9 mm. Hg.

Pressure Gradients and Osmotic Balance in the Lung.—Schleier,[273] on the basis of anatomical measurements in dogs, calculated the probable fall of pressure head in the pulmonary vessels. The velocities on which his calculations

were based were probably too low, and, if these be corrected, his data indicate a probable pressure fall of the order of 10 mm. Hg from the pulmonary artery to the capillary and of 1 mm. from the capillary to the left auricle. Data obtained directly on dogs suggest that, under conditions of real rest, the difference in mean pressure between the artery and capillary is of the order of 10 to 12 mm., and between capillary and vein about 2 or 3 mm. Hg. Schleier's calculations appear to be fairly reliable. The maximal resistance and fall of pressure should be developed in the capillaries themselves. Schleier estimates that over half the total pressure fall occurs in these vessels.

To maintain such a low level of capillary pressure there must be a moderate resistance in the smaller arteries connecting the pulmonary artery with the capillaries. This conclusion is substantiated by direct observation of the pulmonary circulation. It has proved possible to observe the pulmonary capillaries in the mammal under the microscope,[152] and to do this even with the chest closed by observing the lower margin of the lungs through the pleura.[305] Pulsations are visible in the larger arterioles and they are sometimes transmitted to the capillaries, but normally the peripheral resistance is adequate to obliterate them and so produce a steady capillary flow. The capillaries are large and may allow two red cells to pass abreast. The vessels may be seen to contract and the capillaries may become so narrow that even a single corpuscle cannot pass without distortion.

At the most dependent parts of the lungs gravity effects must raise all the pressures, arterial, capillary and venous, and this increase may amount to some 10 mm. Hg. In all capillaries, even the most dependent, the hydrostatic pressure is well below the colloid osmotic pressure of the plasma proteins. Here a balance between capillary and osmotic pressure, such as obtains in peripheral capillaries, must be impossible. Tissue fluid cannot therefore be considered to exist in the lungs, except in the region of the bronchioles which receive their blood from the systemic system and which also have lymphatics. Water must be present extracellularly in the alveoli only as vapor. Lymphatics are absent. Water or saline introduced into the alveoli should be, and is, rapidly absorbed, but fluid formed in the alveoli as a result of raised capillary pressure cannot be removed readily.

The pressure values given above have all been relative to atmospheric pressure. They are valid in considering conditions within the alveoli. When the vessels emerge from the lung into the mediastinal space, where the pressure is subatmospheric, the conditions are altered; the pressures are higher relative to this environment. The heart, contained within the thorax, is also exposed to a subatmospheric pressure, and the pressures developed there must therefore be considered in relation to this standard. A pulmonary arterial pressure which is 27 mm. Hg above atmospheric implies the development within the right ventricle of a pressure which may be greater or less (usually greater) by an amount which depends on the level of intrathoracic pressure. This effect of the subatmospheric intrathoracic pressure, on both the venous and arterial systems, plays an important role in the genesis of respiratory variations in pressure (as will be seen later). It is important in connection with the filling of the auricles.

Disturbances of Osmotic Balance in the Lungs.—From the data already discussed it will be clear that there is a considerable margin of safety preventing the flooding of the alveoli of the lung with tissue fluid. The pressures to which the alveolar walls are exposed

vary with respiration only slightly to either side of atmospheric pressure. The fact that the colloid osmotic pressure of the blood exceeds the pulmonary capillary pressure by some 15 mm. Hg at the heart level gives this considerable margin of safety. The margin is even greater in the highest points of the lung (e.g., the apices in the vertical position), for here the capillary pressure is further reduced by the effects of gravity. At the most dependent parts of the lung the margin of safety is less but still adequate. However, under conditions of failure it is in these areas that the first signs of collection of fluid will be found.

There are two main causes of the development of pulmonary edema: (1) an abnormal rise in pulmonary capillary pressure and (2) an abnormally lowered colloid osmotic pressure. The former is a common accompaniment of cardiac failure. Failure of the left ventricle may necessitate a rise in its diastolic filling pressure. This in turn will demand a higher pressure in the left auricle and consequent increases in the pressures in the pulmonary veins. If ventricular contraction is accompanied by leaks through the mitral valve (mitral regurgitation), the condition will obviously be exaggerated. If in addition there is constriction of the mitral valve by fibrosis (mitral stenosis), the increase in the pressures in the left auricle and the pulmonary veins will be still greater. In this condition the left ventricle cannot be filled adequately without the development of considerable pressures in the left auricle. Any rise in pulmonary venous pressure demands a proportionate increase in the pulmonary capillary pressure to maintain flow. In disease of the mitral valve pulmonary edema becomes a common cause of trouble, particularly at the lowest points in the lung where gravity causes hypostatic congestion. Larger pressure gradients are likely to be required to maintain the more rapid blood flow of activity. Activity can therefore aggravate the development of such congestion and fluid collection. Only by lowering the capillary pressure in the lungs, or by increasing the colloid osmotic pressure is the fluid readily removed.

The second cause of pulmonary edema is lowered colloid osmotic pressure. Usually this is more apt to cause edema in other areas before its effects are noticeable in the lung. If, however, this change is associated with a simultaneous rise in the pulmonary pressures, conditions in the lung may be dangerous. Such, for instance, is the case if a large venous infusion is made too rapidly. The colloid osmotic pressure is rapidly, though temporarily, reduced, while cardiac output and pulmonary pressures are raised. Acute lung edema is peculiarly liable to develop in subjects who are already deficient in plasma protein, and have initially an abnormally low colloid osmotic pressure.

Vasomotor Regulation.—The pressures that have been considered are those of a circulation under conditions of rest. At first thought the presence of vasomotor control appears superfluous. Yet vasomotor reactions have been found in the visual studies of the pulmonary circulation to which reference has been made. Vasoconstriction following stimulation of the stellate ganglion has been observed, and stimulation of the vagosympathetic trunk in the thorax may give either constriction or dilatation. Studies on excised perfused lungs have demonstrated that adrenalin may cause constriction, though, particularly if the lungs are cold, it may produce dilatation.[86] The variable reaction to adrenalin may indicate that both sympathetic vasoconstrictors and adrenergic vasodilators are present. It is uncertain whether there are also cholinergic vasodilators. Pituitrin causes both arteriolar and capillary constriction. Nothing is known of the reflex mechanisms which probably act through this vasomotor control.

During exercise the cardiac output may certainly be increased fivefold, and probably much more than this. It has been shown by Wagner[302] that when the pressure within the pulmonary artery is increased, the effective peripheral resistance is reduced through the passive stretching of the vessels. Consequently in the perfused lung the rate of flow varies not directly with the pressure but more closely with the square of the pressure. Even so a fivefold increase in flow would cause the pressure in the pulmonary artery to rise from a mean value of 20 mm. to one of 45 and the systolic pressure developed in the right ventricle would have to rise to much higher values, which probably

could not be sustained. Vasomotor adjustments would be valuable in adapting the pulmonary circulation to considerable variations in output.

There is no evidence that there is any special control of the pulmonary system independent of that of the systemic. Rather it seems probable that the two systems are involved together in cardiovascular adjustments. The presence of receptors in the pulmonary vessels has been demonstrated histologically and reflex changes have been found to result from variations in the distention of the pulmonary vessels. The whole subject is one which is very difficult to investigate and which is still largely unexplored.

The Blood Reservoir Action of the Lungs.—The passive distention or active vasodilatation of small vessels in the lung must greatly alter the volume of blood they contain. In heart-lung preparations this effect may be measured, and Daly[85] has found that increases in pulmonary pressure that give a 100 per cent increase in flow cause an increased volume of 27 ml. in the lungs of a dog of 11 kilos. A similar increase results from an increased effective pressure (difference in pressure between the pulmonary artery and the thoracic cavity) of 7 mm. Changes in pulmonary blood content in man may, therefore, be considerable, under physiological, as well as under diseased, conditions.

Evidence that variations in the volume of blood contained in the lung may play an important part in the mechanisms of adjustment is indirect. Sjöstrand[285] has estimated the amount of blood in the lung after death in rats of similar weight by analyzing for iron. He found that animals killed suddenly by decapitation showed a lung content of 0.128 mg., but that similar animals killed after violent exercise showed only 0.074 mg. The volume is evidently much reduced. He considers that there exist large sinusoidal veins in which the blood may be stored and which can be contracted and emptied. A similar blood depot function has been assumed on quite other grounds, namely, on measurements of inflow and outflow of blood from the lungs. It is, however, doubtful whether sufficient experimental accuracy is attainable to allow such deductions. The subject must remain open for the present.

RESPIRATORY VARIATIONS IN THE CIRCULATION

Variations in Pressure.—The respiratory movements and consequent changes in intrathoracic pressure cause variations not only in the pulmonary system but also in the aorta and large veins. During inspiration the intrathoracic pressure falls to lower subatmospheric levels (see Chapter XXXVIII). The *primary* effect of a reduction in intrathoracic pressure is a similar reduction in both pulmonary and aortic pressures. The ventricular pressures are developed relative to their own environment, the thorax, and as the pressure is lowered there, the pressures in the large vessels fall correspondingly (Hamilton et al.[156]). But the changes in thoracic pressure have many *secondary* effects. One of the most important is the increase in venous return to the right heart, a result of the increased pressure gradient along the large veins. This increase in inflow assists cardiac filling and, by increasing the outflow of the right ventricle, raises the pressure in the pulmonary artery. As the result of these primary and secondary effects there is an initial fall, followed by a later delayed rise, of pressure in this vessel during inspiration. A similar delayed rise is induced in the aorta, but since the effect is not seen until the increased blood has traversed the pulmonary circulation, the delay may be some three or four seconds. In this connection it is of interest that Visscher, Rupp, and Scott[300] have found that if the inflow to the right heart is decreased by clamping a large entering vein, the resultant fall in aortic pressure occurs only after

just such a delay. These are not the only factors in operation. The inspiratory lowering of thoracic pressure increases the pulmonary vascular bed, lowers the resistance to flow, and increases the volume of blood contained in the lung. The return of blood to the left auricle is, therefore, at first diminished owing to the necessity of filling the increased capacity of the lung. Later, through the lowering of the pulmonary resistance, it is increased above normal. As a result of all these factors acting together, there is a tendency for pulmonary pressure to fall early and to rise late in inspiration. In the aorta the pressure also falls in early inspiration and rises later to reach a maximum after some three to four seconds. This maximum may occur during the middle of inspiration, at late inspiration, or during expiration according to the respiratory rate. In expiration the opposite changes with similar lags are seen. If artificial

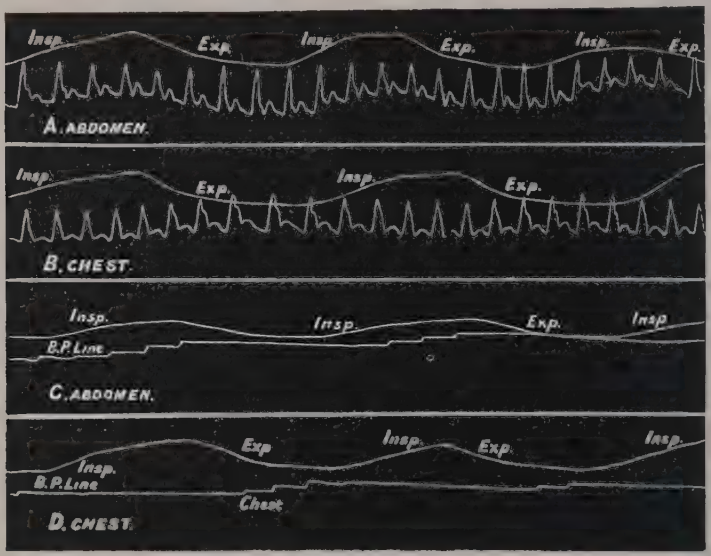


Fig. 200.—Effect of abdominal and chest breathing on the pulse and blood pressure of man. Abdominal inspiration raises the pressure and diminishes the amplitude of the pulse curve. Thoracic inspiration less clearly lowers the pressure. Expiration has the opposite effects. (From Lewis: J. Physiol. 37: 233, 1908.)

respiration by positive pressure is employed, the changes in intrathoracic pressure are reversed (inspiration now gives a rise of pressure), and consequently the changes in blood pressure are also reversed.

Lewis[214] showed that when respiration is thoracic the maximal pressure occurs in middle or late expiration; that when deep abdominal respiration is voluntarily adopted, the maximum pressure develops earlier and the initial stages of inspiration give a rise in pressure instead of a fall. To explain a rise in arterial pressure as the result of inspiration without the lag that would be seen if the effect depended on venous return, one must assume that intra-abdominal pressure is so raised by the extensive descent of the diaphragm that the peripheral resistance in the splanchnic area is increased. The effects obtained are shown in Fig. 200.

Respiratory Variations in Blood Flow.—That not only pressure but flow in the systemic arteries varies with respiration is indicated by such experiments as those illustrated in Figs. 201 and 202. In the experiment shown in Fig. 201 the blood flow in the femoral artery was recorded by the hot-wire method (page 433), but a sensitive galvanometer of slow period, giving records comparable to those of pressure taken with a mercury manometer, was used. The maximum flow in the large arteries was reached in late inspiration and early expiration, the minimum just after active expiration and early in the expiratory pause. If pressures are recorded an entirely similar picture is obtained. The evidence from this and similar experiments is that inspiration produces higher pressures and higher rates of flow and that expiration depresses both to a level below that seen during an expiratory pause. The relations of flow and pressure to respiratory changes are indicated in Fig. 202, though the actual respiratory movements were not recorded. This demonstrates that changes in flow and pressure are comparable.

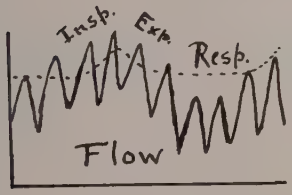


Fig. 201.

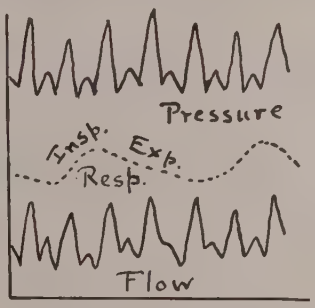


Fig. 202.

Fig. 201.—Flow in the femoral artery (recorded by a sensitive galvanometer of slow period) during a respiratory cycle. The dotted line represents respiration. The solid line represents mean blood flow. (Redrawn from Machella: Am. J. Physiol. **115**: 632, 1936.)

Fig. 202.—Simultaneous records of lateral pressure (upper line) and blood flow (lower line) in femoral artery of a dog. Respiration was not recorded. The respiratory movements, as judged by the blood pressure changes, are, however, indicated by the dotted line. (Redrawn from Machella: Am. J. Physiol. **115**: 632, 1936.)

On the basis of records obtained with the ventricles in a plethysmograph the respiratory variations in blood flow have been considered insignificant.[108] Such a conclusion is not warranted, for the removal of the ventricle from the respiratory variations in intrathoracic pressure, even though the auricles be still exposed to them, creates quite abnormal conditions.

One may conclude that both flow and pressure vary with respiration as the result of many factors, that when the respiratory movements are normal in rate and depth the maxima are reached early in expiration and the minima early in inspiration. The type of respiration as well as respiratory variations in pulse rate modify the picture.

Sinus Arrhythmia.—The variations in pressure and flow that have been described are often associated with a respiratory variation in pulse rate. This variation is particularly marked when the pulse is slow and the vagal tone high. It is usually well marked in the dog, especially when respiration is slow and deep; it is common in children and young people and sometimes detectable in elderly subjects. As in the case of the respiratory variations in blood pressure the relations are difficult to study, for there are usually only four or five

pulse cycles during each complete respiratory cycle. The pulse rate of a subject who happened to have a normal respiratory rate of six per minute or less and consequently had many pulse cycles in each respiration is shown in Fig. 203. The record demonstrates that the pulse rate was accelerated with the commencement of inspiration, but was slowed again before inspiration was completed, and reached its minimum rate early in expiration. During the long expiratory pause the pulse rate increased gradually and then showed a more rapid rate of increase with the next inspiration. Clearly there were here at least two active phases: an increase in rate contemporaneous with the start of inspiration, and an active slowing below the average rate starting in inspiration and lasting through expiration. The former is always seen and is generally recognized; the latter is usually assigned an expiratory cause, which certainly cannot have been the case in this subject. The reversal from an increased to a decreased pulse rate during inspiration may have depended on a reflex induced by the depth of inspiration, or by the rise in blood pressure which accompanied

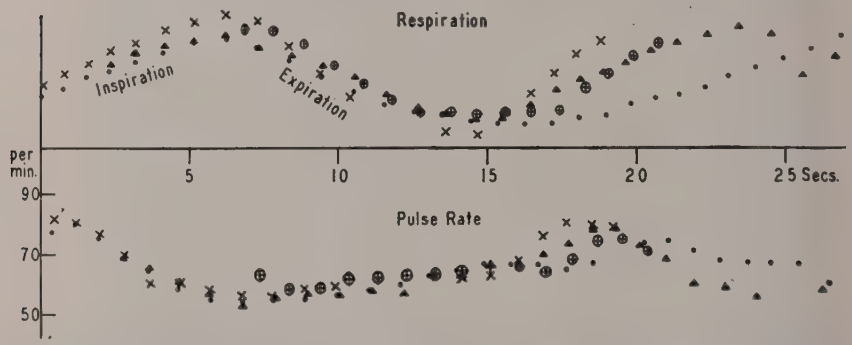


Fig. 203.—Relation of pulse rate to respiration in a subject with a slow breathing rate. The various symbols indicate individual respiratory cycles. (From unpublished observations by M. E. Maxfield and M. D. Blithe.)

it, acting secondarily through the carotid sinus. In this subject such an inspiratory rise of systolic pressure could be demonstrated, but it was not marked. The resemblance of the relationship between pulse rate and respiration to that between blood flow and respiration (Fig. 202) is very noticeable.

To some extent the changes in blood flow are certainly dependent on those in pulse rate. The pulse rate changes are evoked almost entirely through the vagi, for they disappear almost completely when these nerves are divided. Under such conditions the respiratory variations in blood flow are also much reduced despite the increased depth of breathing which results (see page 574). The effects of respiration on the pulse pressure and on the different times of development of the maxima and minima of systolic and diastolic pressures are also dependent on changes in pulse rate. Normally, the maximal and minimal levels in the respiratory variations of diastolic pressure are reached one or two pulse cycles earlier than the corresponding maxima and minima in systolic pressure.

The causes of sinus arrhythmia are complex. It has been shown by Heymans[170] that if the head of a dog be connected with its trunk by the vagi only, and be perfused from

another dog, there may be respiratory movements (nasal, etc.) in the isolated head which are entirely out of time with that of the artificial respiration of the trunk. The cardiac arrhythmia is found to follow the head rather than the trunk rhythm. One cause of the arrhythmia is, therefore, an effect of the respiratory center on the tonic vagal center which regulates the heart rate. But it has also been shown that distention of a single lung in artificial respiration may cause an increase in cardiac rhythm if the nerves are intact, and that a similar distention of the opposite lung after denervation is without effect. The effects of distention in the innervated lung are produced even if the branches of the pulmonary artery to that lung are ligated. An increase in rhythm induced reflexly from the lung through the vagus is, therefore, also a factor, and it has been shown that if the distention of the lung is extreme, the effect is reversed and the heart may be slowed.[268] In the intact animal any increase in venous return is likely to exaggerate the increase in rate through the Bainbridge reflex[18] and any rise of blood pressure late in inspiration is likely to slow it through the carotid sinus reflexes. If in a dog with marked sinus arrhythmia the chest be opened, so that neither changes in intrathoracic pressure nor any movements of the lung can occur, the sinus arrhythmia continues to accompany the respiratory movements, but it is less marked than previously; sectioning of the phrenics decreases it still further but does not abolish it. Probably, therefore, many factors are concerned in the production of the arrhythmia in the intact animal (see discussion by Anrep[18]).

Effects of Large Variations in Intrathoracic Pressure.—When a subject exerts marked suction, as, for example, in sucking fluid up a tube, the intrapulmonary pressure is subatmospheric, and the intrathoracic pressure is lowered

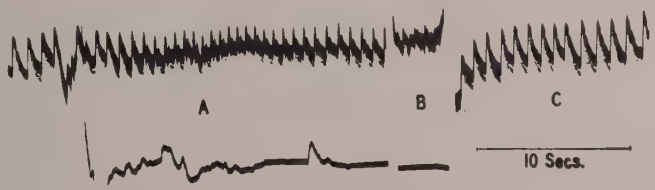


Fig. 204.—The effect of raised intrathoracic pressure on the pulse. *A*, pulse rate before and during the first twenty seconds of expiration against a pressure maintained fairly steadily around 40 mm. Hg (lower record of *A* and *B*). *B*, pulse rate during the period between the fiftieth and fifty-third seconds of the forced expiration. *C*, record from the sixth to the eighteenth second following the end of exertion of expiratory pressure. (From unpublished experiments by H. C. Bazett.)

by an equivalent amount. Not only is air sucked in through the mouth, but a sucking force is exerted on the intrathoracic vessels, and venous return is improved. The opposite is true when expiration is carried out forcibly against a resistance. A pressure of 80 to 200 mm. Hg or more may be exerted by raising the diaphragm through voluntary compression of the abdomen. If this be maintained with an open glottis, it causes such a high intrapleural pressure that the circulation stops and the individual faints. During the first few seconds, however, the blood in the lungs is emptied into the left heart and the expiratory pressures may be maintained for a short time. The effect of raised intrathoracic pressure on the circulation is well demonstrated by the experiment of holding one's breath while blowing against a mercury manometer to keep it at a pressure of 40 mm. Hg. This creates a positive pressure in the thorax of some 30 to 35 mm. Hg, and interferes with venous return. It has been used as a test for fitness and is commonly known as the Flack test.[117] It tests at one and the same time the respiratory efficiency (capacity to hold the breath) and the ability of the vascular system to effect a venous return under the conditions of a high intrathoracic pressure. It also provides a useful

psychological test in that the observer can readily detect whether the subject is attempting to perform the test to the best of his ability or is malingering in an attempt to prove himself unfit.

The subject takes a deep breath and blows the mercury column to 40 mm., and then holds it there to the best of his capacity. For the first few seconds the pulse is slow or normal in rate and full; after this it becomes rapid and feeble as venous return falters. As adjustments are effected in some unknown way, the pulse returns almost to its original value and then later, often after thirty to sixty seconds, becomes small and rapid; finally, it may slow again and becomes quite small and eventually impalpable.

A subject who is doing his best gives up either from respiratory or circulatory failure. If the trouble is respiratory, variations are shown in the manometer record before he gives up, and hyperpnea occurs afterwards. When circulatory failure is the determining factor, the pulse becomes impalpable several seconds before the end. If a subject has a three-minute rest and then repeats the test, he can always exceed his previous time. Anyone who is not trying or is malingering does not expect this, and is unable to judge the time. He cannot, therefore, mislead an examiner. The pulse response may be readily judged by palpation, particularly if a record be kept of the number of beats in each five-second period. The sort of response obtained in a normal person is shown graphically in Fig. 204.

CHAPTER XXXVI

THE BLOOD SUPPLY OF CERTAIN ORGANS

The blood supplies of the liver, spleen, heart, and brain present certain peculiarities, and must receive special consideration.

THE HEPATIC CIRCULATION

The liver receives blood not only from the hepatic artery in which the blood is at high pressure, but also through the portal system which supplies venous blood that has already passed through the capillaries of the gastrointestinal tract or through the spleen. Pressures in the portal vein are quite low. The hepatic arterial supply exists to insure an adequate amount of oxygen for the liver; probably it is regulated in accord with the need for oxygen. Blood from each stream leaves the liver through the hepatic veins. The pressure within the terminations of the hepatic artery is apparently lowered by resistance to a level at which it does not interfere with the flow of portal blood into the liver. The hepatic arterial and the portal venous streams meet in the lateral portions of the liver lobules where they enter the sinusoids. Proceeding through these wide channels to the center of the lobule this mixed blood enters the branches of the hepatic veins. From here it is collected into larger veins and after a short course joins the inferior vena cava. The portal blood, therefore, passes through two capillary systems. It is obvious that in both of them it cannot exert a pressure which balances the full colloid osmotic pressure of the plasma. The pressure in the mesenteric capillaries has been shown to be about 26 mm. Hg. In the portal vein the pressure is only 6 to 12 mm. Hg (8 to 16 cm H_2O), the flow is slow, and kinetic energy is insignificant. The pressure in the liver capillaries must be quite low. Since the pressure in the hepatic vein is close to the atmospheric level, the pressure in the liver capillaries is somewhere between 5 mm. and zero.

It has been shown by McMichael[225] that if the mesenteric veins are clamped and inflow to the portal system is obstructed, the pressure in the portal vein above the clamp falls to about 3.7 mm. If the hepatic artery be also clamped, it falls still lower (to about 2.7 mm.) but not to zero. Under such circumstances the pressure maintained should be that of the osmotic pressure of the proteins, and the low value implies that the effective pressure is only 3 or 4 mm. This is entirely in agreement with Starling's observation[286] that lymph is formed in the liver with great ease and that it contains almost as much protein (6 per cent) as does the blood plasma. The condition, therefore, appears to be one in which the capillary pressure is about 3 mm., and where the wall is so permeable to colloidal particles that the effective osmotic pressure of the plasma proteins is reduced to this level.

The portal system functions not only in digestion and absorption but probably also as a blood reservoir. This was emphasized by Krogh.[204] He visualized the hepatic vessels as offering a more or less constant resistance to flow, with a variable resistance in the mesenteric vessels. When arteriolar re-

laxation occurs in the latter, the increased blood flow would tend to dilate the vessels in the portal system. Similarly, when the mesenteric vessels constrict, the portal system would be relatively empty and the extra blood would be available for use elsewhere. To such a view must be added the probability that vasomotor mechanisms can also produce active constriction of the veins; the portal vein has a heavy muscular coat.

The conditions in the system are complex. It is possible that the branches of the hepatic artery and portal vein join before these vessels reach the sinusoids of the liver. The hepatic artery is variously estimated to deliver ⅙ to ⅓ of the total blood supply. The *pressure* in the portal vein is probably modified by the amount of blood added in the liver by the hepatic artery, as well as by the rate blood is delivered to the peripheral end of the portal system through the mesenteric arteries. The *amount* of blood contained in the system must be determined by the pressure and the elasticity constants of the system; the latter must vary with the tone of the vessel walls. The volume of the liver depends on its contained blood. The part of this which is in the portal system may be varied by the degree of constriction of the radicles of the portal vein, the part in the hepatic veins varies with the pressure in the inferior vena cava and consequently with the conditions of cardiac filling. The liver also has a muscular-fibrous coat, Glisson's capsule, and variations in the tone of these muscle fibers may alter the volume of the viscus.

Splanchnic stimulation causes an immediate rise in pressure in both the inferior vena cava and the portal vein and an increase in the volume of the liver.[100] Although arterial pressure is raised, back pressure effects from the ventricle fail to explain the immediate rise in pressure which occurs.

The radicles of the hepatic vein may, by constricting, empty blood into the vena cava and also cause an increased resistance to portal flow. This might give rise to congestion of the liver by back pressure. Isolated segments of veins of the portal system and of the inferior vena cava (of which the hepatic vein is a branch) have been shown to constrict to adrenalin.[100, 128] The situation is complex, for intravenous injections of adrenalin produce not an increased but a decreased volume of the liver.

Many attempts have been made to analyze the complicated situation in the liver.[196, 225] The effects of drugs have been investigated by Katz and Rodbard[196] by methods which recorded arterial, vena caval, and portal venous pressures and also the rate of flow through (1) the portal vein, or (2) the inferior vena cava above the liver, or (3) the inferior vena and the portal vein together, when the latter was shunted, so that the blood did not pass through the liver. These workers point out the analogy between the conditions in the portal circulation and those of the venous supply to the heart. Their statements are illuminating and may be quoted. In discussing the venous return to the heart they write: "The cause for a change in venous pressure can be determined only when information regarding the rate of venous flow is also known. Thus an increase in flow coincident with a rise in venous pressure indicates the inability of the heart to cope with the increased venous return, while a coincident decrease in flow indicates a rapidly failing heart. A decrease in venous pressure can be similarly analyzed. When it is coincident with an increased venous flow, it indicates an improved cardiac action, otherwise it indicates a decrease in venous return occurring either during the dilatation of the peripheral bed, or because of an increased resistance to flow in that bed."

Katz and Rodbard have extended their analysis to the portal pressure as follows: "Thus a rise in portal pressure with an increased portal flow indicates the dominance of a greater return of blood from the preportal area either during the period of shrinkage in its bed, or because of a decrease in its resistance to flow. The reverse is true when portal pressure and flow decline. A rise in portal pressure with a decreased portal flow indicates the dominance of increased resistance in the liver. It may be noted that the increased resistance of the liver may occur at several sites: (a) the sphincters of the hepatic vein at its junction with the vena cava, (b) the sphincters shown by Knisely to exist near the central veins within the liver, (c) sinusoids within the liver, (d) the intra-hepatic terminals of the portal vein or (e) an increased flow via the hepatic artery because of a rise in systemic arterial pressure or dilatation of the intra-hepatic terminals of the hepatic artery." This citation will indicate the complexity of the system and the difficulty of exact analysis. Katz and Rodbard conclude that adrenalin injections cause constriction of the

preportal splanchnic vessels resulting in a decreased inflow into the portal system, as well as a more marked constriction of the liver vascular bed. The two processes are not synchronous. The portal flow decreases, portal pressure falls, and the liver volume shrinks. Hepatic vein sphincters must be relaxed, for the outflow through the hepatic vein is increased. Later there is an increased portal flow with an increased portal pressure probably due to an increased inflow from the splanchnic vessels at a later stage.

Pitressin raises arterial pressure by contracting the smooth muscle of the systemic and preportal vessels. There is a diminution in portal flow, portal pressure, and liver volume, all apparently dependent on the marked splanchnic vasoconstriction. There may be an increased pressure in the vena cava, but it is small and probably dependent on decreased cardiac output.

Histamine in doses exceeding 50 gamma causes in the dog constriction of the radicles of the hepatic vein, thus producing obstruction to hepatic outflow, increase in liver size, slowing of the portal flow and rise in portal pressure. These actions tend to *reduce* venous flow and pressure in the inferior vena cava. The vessels of the hepatic system are less sensitive than the peripheral vessels to smaller doses of histamine. With such doses the peripheral vessels dilate and cause a decrease in arterial and a rise in inferior caval pressure.

Acetylcholine causes a fall of arterial pressure from peripheral vasodilatation. There may be a fall of portal pressure from stasis in the splanchnic system; there may also be marked constriction of the regulators of the hepatic vein with rise in portal pressure. In either case portal flow is reduced.

These complicated reactions are probably of importance in the blood reservoir function of the portal system. Attention has been drawn to the large volume of blood contained in the portal veins. Changes of the type described must be able to induce considerable changes in the blood contained within the liver and portal system. Much additional work is required to determine the exact conditions under which these complicated reactions are called into play.

At the junction of the esophagus with the stomach and between the liver and the diaphragm anastomoses exist between veins of the portal system and the main systemic vessels. There are also anastomoses between branches of the inferior mesenteric vein and branches of the internal iliac veins. Thus when the flow through the liver is partially obstructed a considerable collateral drainage of the portal system may develop.

THE SPLENIC CIRCULATION AND THE BLOOD RESERVOIRS

A large volume of noncirculating blood may be held in the spaces of the splenic pulp. The capsule and trabeculae of this viscus contain smooth muscle the contraction of which diminishes the volume of the organ and forces the contained blood into the splenic vein, a branch of the portal system. Splenic contraction may be induced by adrenalin and by impulses in the sympathetic fibers which supply the organ. The spleen may be involved in reflexes from the carotid sinus and aortic arch and in the pressor reflexes of the spinal animal (pages 463 and 472). The significance of the splenic response in these reactions appears to be the increase in the effective blood volume and the consequent improvement in venous return that result from the contraction. But the spleen is by no means the only blood reservoir. The portal system of veins, including those in the liver, forms another, and conditions in which the spleen is contracted appear also to be associated with contraction in other parts of the splanchnic system. This may be demonstrated in an exteriorized colon.[23] The possibility that storage of blood may take place in the large pulmonary veins has been discussed. Large veins all over the body, and probably also the large arteries are potential reservoirs, since their size may be reduced and the volume of blood saved be put into circulation elsewhere with very little increase in the resistance to flow. Such reservoirs are particularly needed when large arteriolar and capillary areas are dilated, as in muscular exercise. It is during exercise that splenic contraction normally plays a conspicuous rôle. The reser-

voirs are also of great importance under less normal conditions where the blood volume is reduced, as after hemorrhage.[21] Here other reservoirs, such as the veins and venules of the skin surface, may be called into action.

THE CORONARY CIRCULATION

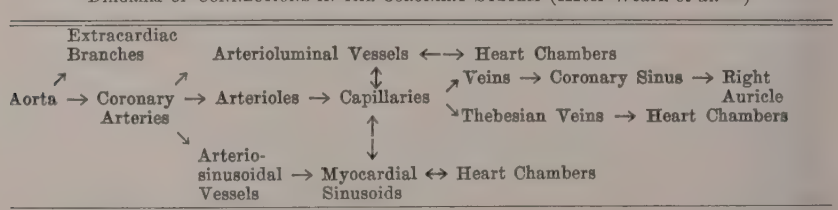
Anatomical Considerations.—The blood supply to the heart is delivered through the two coronary arteries which arise from the aorta just above the semilunar valves. The broadening of the stream at the origin of the aorta due to the sinuses of Valsalva creates eddy currents which hold the leaflets of the valves floating in mid-stream. The orifices of the coronary arteries consequently remain open during the entire cardiac cycle, and these arteries are fed by the lateral pressure of the aorta. Branches from these vessels ultimately penetrate the muscle to supply the deeper layers of the heart. These deeper smaller vessels are exposed to compression as the heart contracts, to considerable compression in the left ventricle, and to much less in the right ventricle. The compression pressure developed within the ventricular cavities is obtained by the effect of a series of concentric fibers. The effect of this serial arrangement may be compared with that of a number of electric batteries connected in series. Only in the innermost layers can the pressures to which the coronary branches are exposed approach that developed within the ventricle.

The outflow from the coronary arteries is mainly returned to the right auricle through the large coronary vein ending in the coronary sinus, but a part passes through numerous small veins which open directly into the right auricle. Thebesian veins, however, exist throughout the heart and connect with all its chambers; through these blood may return under suitable pressure conditions into any of the chambers.

The pathways through the heart are complex. Anastomoses between the coronary arteries and extracardiac branches of the aorta exist, particularly round the junctions of the large veins with the heart. Arterioluminal vessels connect the coronary arteries directly with the cavities of the heart, and arteriosinusoidal vessels connect with myocardial sinusoids, and through them again with the heart cavities. Thus there are at least four different paths through which the blood can pass from the arteries back to the heart. It seems probable that some of these paths can conduct blood in either direction. The complex arrangements and the probabilities of the direction, or directions, of flow involved have been expressed by Wearn and his co-workers in the form of a table (see Table XVI).

TABLE XVI

DIAGRAM OF CONNECTIONS IN THE CORONARY SYSTEM (After Wearn et al.[305])


Extracardiac Branches
Arterioluminal Vessels ←→ Heart Chambers
Aorta → Coronary Arteries → Arterioles → Capillaries
Veins → Coronary Sinus → Right Auricle
Thebesian Veins → Heart Chambers
Arterio-sinusoidal Vessels → Myocardial Sinusoids ↔ Heart Chambers

Pressures in the Coronary Vessels.—The pressure in the coronary arteries at their origin from the aorta is the lateral pressure of the aorta. The pressure

more peripherally is definitely lower. If a large branch of a coronary artery be clamped, the pressure developed peripheral to the clamp is that derived from other branches by anastomoses or from the ultimate connections of the artery with the heart cavities. Measurements of pressures in clamped coronary arteries have been made by Wiggers and his collaborators. The same group have also measured the absolute resistance to flow in peripheral branches during both ventricular systole and diastole. This was achieved by determining the pressure which must be delivered to such a vessel in order to produce a flow of blood. The resistance so determined must vary according to the distribution of the branches at different depths in the ventricular wall. Normally pressures which exceed 0.8 of the intraventricular pressure are able to produce some flow even at the height of ventricular systole. This method of investigation is able to demonstrate that the peripheral branches of the arteries are exposed to compression during ventricular contraction. The compression not only increases the resistance to flow but also must displace blood from one part of the arterial system to another less exposed to compression.

The pressure in the coronary vein cannot differ much from that in the right auricle, and must therefore be of the same order as that in other large central veins.

Coronary Flow.—The total flow in the coronary system is not easily determined. Inflow through a branch of one coronary artery may be measured, and the total flow through the whole system estimated. Or sample measurements may be made of the venous flow back to the auricle in the coronary sinus. It is believed that under normal conditions about $\frac{3}{5}$ of the total return flows through this vessel, but there is abundant evidence that the ratio of flow in this vessel to total flow is not a constant.[193] Again, the work performed by the heart may be estimated, and the amount of oxygen the heart must consume to do this work at a common level of muscular efficiency may be calculated. For any determined unsaturation of venous blood returning in the coronary system the total outflow may thus be calculated. By such methods the coronary blood flow has been estimated as 0.5 to 0.75 ml. per gram of heart muscle per minute. Under ordinary basal conditions this would imply in man a flow of about 5 per cent of the total cardiac output or some 200 ml. per minute in an average sized individual. When the work of the heart is increased, the flow must be much greater. Measurements of coronary flow have been made in dogs by the use of a Rein thermostromuhr applied aseptically. Such measurements give a good indication of the magnitude of variations. Increases in flow amounting to four times the resting level are found with exercise.[105]

Phasic Variations in Coronary Flow.—Blood flow may be measured with the Rein thermostromuhr, but recording instruments of this kind situated outside the arteries are unable to record the phasic variations during the cardiac cycle. These variations depend on the complex interrelationships of the variable aortic driving pressure to the variable resistance in the peripheral vessels which is induced by their compression during muscular contraction. The hot-wire system used by Machella[226] can be applied, but it is not readily standardized. Such a system was originally used by Anrep[10] to investigate coronary flow, but the hot wire was not in the blood itself but in an air system connected to vessels used to deliver blood to, or collect blood from, the heart. The use of a thin wire within the lumen of the coronary vessel itself allows a better estimate of phasic variations in flow. Records so obtained[226] are shown in Fig. 205. It will be noted

that they indicate a rate of flow which is depressed during ventricular systole, rises gradually to a maximum in diastole (*A*), or rises rapidly to a high plateau in diastole (*B*). The onset of ventricular contraction in the period of rising tension appears to hinder, but not to prevent, flow. With the rise of pressure in the aorta after the aortic valves open flow is again temporarily improved, but in spite of the pressure rise in the aorta the rate of coronary flow decreases during ventricular systole. Such direct records confirmed the earlier estimations of phasic changes in flow made by Anrep, Wiggers and others on the basis of less direct evidence.

Much of our knowledge of coronary flow and the factors which affect it has been derived from the brilliant analyses of coronary pressure made by Wiggers and his associates. It has been pointed out that they measured not only the pressure in the peripheral branches of the coronary arteries, but also the resistance

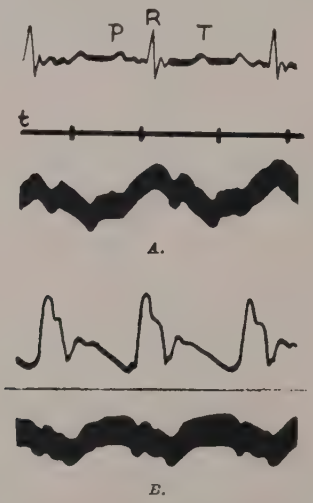


Fig. 205.—*A*, Record of flow in the anterior descending branch of the left coronary artery (lower curve) and electrocardiogram—Lead II—(upper curve). Time in 0.2 second is indicated by *t*. (Note that with this method the velocity curve is logarithmic and minimizes the higher velocities; a downstroke indicates a decrease in velocity.) *B*, Record of flow in the coronary artery as in *A* (lower curve), with a simultaneous record of the pressure in the carotid artery. Note decrease in velocity at the time of the upstroke of carotid pressure. (*A* and *B* represent redrawn records from Machella: Am. J. Physiol. 115: 632, 1936.)

to flow in these branches at different phases of the cardiac cycle. Records of central and peripheral pressures in the coronary system of a dog are indicated in Fig. 206 (curves A and B). Curve C represents curve B adjusted in relation to the apparent resistance to flow as separately determined. From the difference in pressure between A and C both the rate of flow along the coronary artery and its phasic variations are estimated. The deduced values are shown in D. It will be noted that this curve in the set of records labelled I is very similar to that of Fig. 205, *B*. Under normal conditions the flow in diastole is considerably greater than that in systole. Under abnormal conditions (as in aortic regurgitation) where diastolic pressure is low and systolic pressure is high, the greater proportion of the flow may occur in systole (see Fig. 206, *II*). In

Part *II* of Fig. 206 the derived curve D, representing flow, is quite different in shape, though it still shows the evidence of increased resistance to flow during systole.

The phasic variations in flow have recently been measured more precisely and directly.[148, 149] The curves deduced indirectly have been thus demonstrated to be true in broad outline, though quantitatively they are inaccurate. In this series of researches (also from Wiggers' laboratory) the flows deducible from the pressure changes have been compared with flows through a coronary artery perfused with blood delivered through a flow meter from a reservoir at constant pressure. This latter method has the disadvantage that the feeding pressure is constant, whereas normally it undergoes fluctuations. Consequently, measurements were also made when the coronary artery was supplied from the subclavian artery, again with passage of the blood through a meter. Such studies have demonstrated that flow through a coronary artery may not indicate exactly the rate of flow through the intramural vessels. Owing to the changing pressures

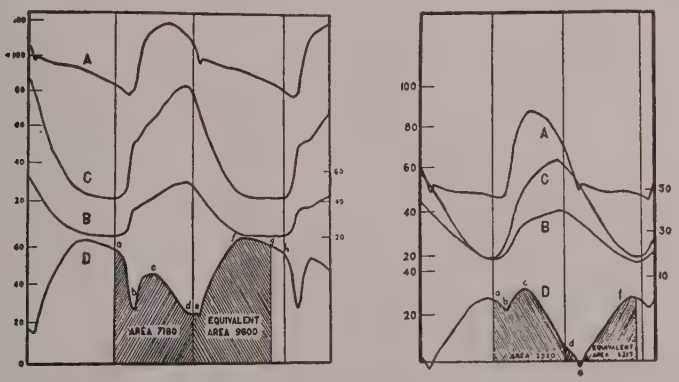


Fig. 206.—*I.* Records (to scale) of pressure in the aorta (*A*) and in the peripheral end of the anterior descending coronary artery (*B*). The latter is corrected to give correspondence with the separately determined resistance to flow in this vessel (*C*) during the cardiac cycle. The flow *D* is estimated from the difference between *A* and *C*. Compare curve *D* with that of Fig. 205 *A*. The areas below curve *D* represent the relative volume flow in the systolic and diastolic phases.

II. Records obtained as in *I*, but under conditions of low diastolic pressure and high pulse pressure. Systolic flow exceeds diastolic flow. (From Green, Gregg, and Wiggers: Am. J. Physiol. **112**: 627, 1935.)

within and the changing compression pressures without the vessels, there is an appreciable transfer of blood from one part of the system to another and a temporary storage of blood in distended superficial vessels. The records indicate that the intramural flow in diastole soon reaches its peak and then declines slowly as the aortic driving pressure falls. During systole there is a sudden retardation of flow with the onset of isometric contraction, and an increase as the aortic valves open and aortic pressure rises. The rates of flow into the coronaries at the end of systole and at the end of diastole probably represent the respective systolic and diastolic levels of intramural flow. At these points the complications introduced by alterations in the reservoir capacity of the main vessels are minimal. The resistance to intramural flow appears to be two to four times as great during systole as during diastole.

The Regulation of Coronary Flow.—In the denervated heart-lung preparation Starling found that the coronary flow is proportional to the aortic pressure and may be modified by systemic arterial resistance, but he found that it is unaffected by changes in cardiac output. The peripheral resistance of the heart-lung preparation is so abnormal and its reduction in systole by stretching of the artificial peripheral bed is so great and so unlike conditions in the actual circulation, that conclusions based on his results must be guarded.

Certainly in the intact animal the flow is determined by the mean level of pressure during systole and diastole, particularly the latter. It is also affected by the resistance to flow offered by the coronary vessels themselves These vessels may be dilated reflexly and through the action of chemical metabolites. The chemical effects may even be demonstrated in the heart-lung preparation.[174] Reduction of oxygen in the coronary blood produces the enormous in-

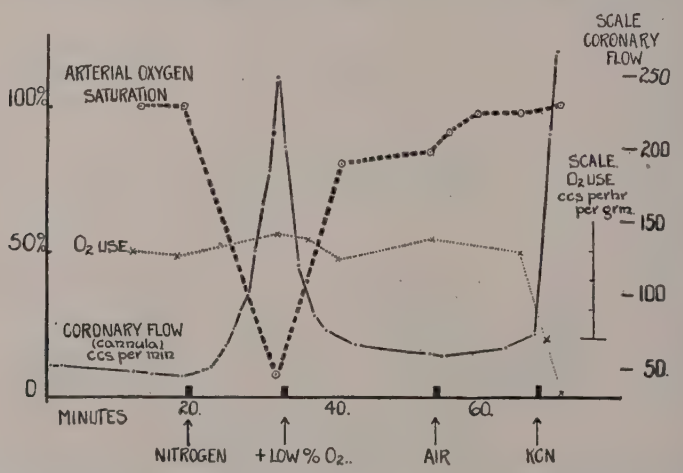


Fig. 207.—Relation of flow in coronary vein to oxygen saturation of arterial blood and oxygen consumption of the heart. Heart-lung preparation. Effects of ventilation with nitrogen, air with low oxygen content and ordinary air and addition of KCN to blood. (From Hilton and Eichholtz: J. Physiol. 59: 413, 1925.)

crease in coronary flow indicated in Fig. 207. This increase occurs whether the oxygen lack results from inflation of the lungs with nitrogen or from the addition of KCN to the perfusing blood. In the former instance no great increase is observed unless the oxygen saturation of arterial blood falls below 50 per cent, yet it may be noted that even when the oxygen content is below this level the heart obtains its full quota of oxygen. Evans has shown, by analysis of blood from the coronary sinus, that the heart is able to remove all the oxygen from blood; the blood may emerge from the coronary veins completely reduced. Carbon dioxide added to air in the lungs produces a slight increase of coronary flow, but no such increase as that obtained during anoxemia. The addition of lactic acid to the perfusing blood also produces only small effects. Other metabolites, possibly a histamine-like substance, may be concerned in the reaction to anoxemia.

Much experimental work has shown that the coronary vessels are under nervous control. They are richly supplied with nerves of vagal and sympathetic origin. Section of the vagi increases the flow through the coronaries, even when the blood pressure remains unchanged. Stimulation of the vagi decreases the flow. Stimulation of the stellate ganglion and intravenous injection of small doses of adrenalin increase the coronary flow. Thus it appears that the vagus causes constriction, the sympathetic dilatation of these vessels. In the intact animal coronary flow varies with cardiac work, but whether this regulation is accomplished mainly by chemical or mainly by nervous control is not known.

The analysis of coronary inflow by the methods previously described also gives evidence of considerable variations in the total flow. There is a considerable increase in flow if the work of the heart is increased either by an elevation of blood pressure or by an increased cardiac output. A reduction in the blood viscosity by injection of saline also increases the rate of flow. A period of ischemia of the coronary bed greatly increases the rate of flow during the period immediately following the restoration of the circulation. By all methods of examination there is, therefore, evidence that the flow varies not only with the aortic pressure but also with the conditions of the peripheral vessels as determined by reflex or chemical factors. There is no evidence that the rate of coronary flow shows as great variations as the amount of work the heart has to perform. The reserve oxygen carried by the blood must be used for meeting emergencies, and under experimental conditions venous blood can be obtained from the coronary sinus which is entirely devoid of oxygen. Yet the heart continues to contract. It is therefore not surprising that in the presence of diseased and partially obstructed coronary arteries, ischemic conditions accompanied by stimulation of nerves mediating pain (angina pectoris) may be induced by exercise. Since such damaged vessels may be unable to adjust themselves according to the resistance imposed by the viscosity of the blood, it is reasonable to suppose that variations in blood viscosity may be very important in such individuals. In the adjustments associated with any sudden decrease in blood volume (other than diseases due to hemorrhage) there is usually a relatively greater decrease in plasma than in cells, and consequently blood viscosity increases. Such changes in viscosity may lead to a significant decrease in flow through abnormal coronary vessels.

THE CEREBRAL CIRCULATION

The brain and spinal cord are peculiar in that they are enclosed in a bony box, in which they are supported by cerebrospinal fluid. In the vertebral canal the central nervous tissue is also cushioned by fat. The total volume within the bony box cannot alter. Even if bone be removed, the intact dura forms an inelastic envelope. Changes, however, can develop in the distribution of blood from arteries to veins and vice versa. Further modifications in the space occupied by blood as compared with that taken by either extracellular cerebrospinal fluid or intracellular water can occur. It is therefore possible to induce considerable changes in the resistance to flow. A dilatation of arterioles can occur and reduce the resistance, and the extra space so required for the arterioles may be provided by reduction in the lumen of the large veins. Such changes in the veins have scarcely any appreciable effect on the venous resistance to flow.

It is essential for the organism that an adequate supply of blood to the cerebrum and spinal cord be maintained. For the most part this is attained by subordinating the control of the whole circulation to this end. The system is arranged so that the flow is dependent on the pressure within the large arteries. If this level is maintained, an adequate flow is ensured under most conditions, for the cerebral vessels themselves are less affected by nervous and chemical controls than are other vessels. The regulation of the blood pressure level by intrinsic vascular reflexes must therefore be considered as one of the most important safeguards adopted to maintain the cerebral circulation.

While the circulation to the brain is mainly guaranteed by the maintenance of an adequate feeding pressure in the arteries, local variations in peripheral resistance do occur. Owing to the limitations imposed by the enclosure of the central nervous system in an inelastic box no general dilatation of all the vessels at one time is possible. Any dilatation in one area must be balanced by a reduction in the volume occupied by (a) some other area, (b) by the large veins, or (c) by the cerebrospinal fluid. Variations in the degree of tonic contraction of vessels play a much smaller part than in other organs. The vessels of the dura mater, however, can constrict considerably in response to sympathetic stimulation and to injection of adrenalin. Dural vessels observed through a window inserted in the skull may be seen to undergo a reduction in diameter of 30 per cent or more, a change not much less than that which may occur in skin vessels, but standing in contrast to the much smaller changes shown by the vessels of the pia mater which actually carry blood to the brain.

The tone of the pial vessels is less affected by nervous than by chemical factors. Constriction or dilatation can be brought about by nervous influences, but they are usually initiated by chemical changes.[324] Measurements of the rate of blood flow have been used by Schmidt and his associates[275-277] to determine variations in peripheral resistance in the brain; the resistance must be lowered if the flow is increased without a rise in arterial pressure. Blood flow has been determined by measuring the heat delivered by the blood to a cooled rod embedded in brain tissue; an increased flow of blood transports more heat to the rod. Using these methods Schmidt and his associates could find no evidence of nervous control of the vessels which are distributed in the medulla.[277] On the other hand, the resistance offered by these vessels varied greatly according to the tension of CO_2 in the blood. High concentrations of CO_2 produced dilatation and subnormal concentrations, constriction. The vasoconstriction produced by a low level of CO_2 (acapnia) and the resultant decreased rate of blood flow through the vessels in the medulla are indicated in Fig. 208. The vessels of the pia mater are also sensitive to other chemical substances; acetylcholine, alcohol, ether, histamine, and nitrites produce dilatation. Oxygen has some constrictive effect, and dilatation develops in its absence.

In the cerebral cortex the same chemical control of the blood vessels is seen, but it is less dominant. Nervous control is also present. The existence of both controls may be shown by the methods used by Schmidt. They may also be demonstrated by utilizing a window set in the cranium through which reactions of the pial vessels can be followed with a microscope.[126] Vasoconstriction is produced by electrical stimulation of the cervical sympathetic; the response is strictly ipsilateral. It is usually limited to arteries of intermediate size (diameter greater than 50 microns). Occasionally constriction may be seen in arterioles, venules, and veins. No change is detectable in capillaries. The

change in the size of the vessels is small (only about one-tenth of that which may occur in vessels to the skin). The vasoconstrictor nerves appear to be adrenergic, though intravenous injections of adrenalin usually produce an increase, not a decrease, in the size of the vessels. This is probably due to the effect of the rise in arterial pressure (the feeding pressure), overbalancing the small local constricting effect of adrenalin. There is no evidence of any vasoconstrictor tone, since no dilatation of the vessels is seen when the cervical sympathetic nerves are severed.

A reflex dilatation of the vessels in the pia mater can also be obtained. The efferent mechanism may be activated by electrical stimulation of the geniculate ganglion of the seventh nerve. Dilatation is strictly ipsilateral. Dilatation of the vessels supplying an active area of the cerebrum can be demonstrated; for instance, there is an increased rate of blood flow to the visual area of the cortex when the retina is exposed to light. Whether this is due to a nervous or to a chemical control is uncertain. Forbes has also described a marked dilatation of the cerebral vessels in response to a fall in arterial pres-

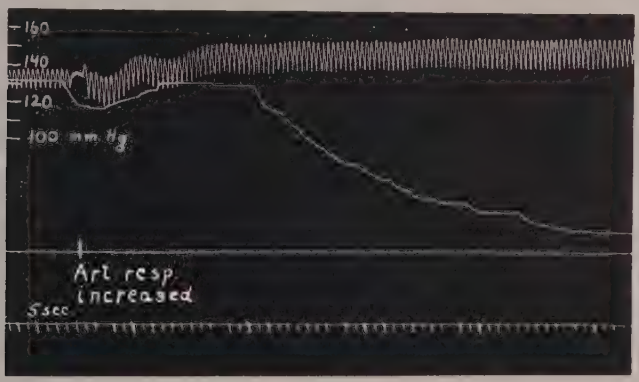


Fig. 208.—Effect of increasing artificial ventilation in curarized cat on blood pressure (upper record) and blood flow through the medulla (lower record). (From Schmidt and Pierson: Am. J. Physiol. 108: 241, 1934.)

sure below a critical level of some 70 to 80 mm. Hg. This may be chemical in origin and dependent on asphyxial metabolites formed in the tissues. However, a reflex causation cannot be excluded with certainty. Stimulation of afferent nerves which commonly induce reflex dilatation in the body as a whole, such as the aortic or carotid sinus nerves, does not produce any detectable effect on the central vessels except passive effects due to the changes in general arterial pressure.

Much of the investigation of the blood flow to the cerebral cortex has been carried out by Forbes with the cooperation of others including H. G. Wolff, W. G. Penfield, and S. Cobb. These workers have utilized the "window" technique to a considerable extent. In a summary of our knowledge of the physiological regulation of cerebral blood flow Forbes[126] concludes that the extracerebral control of arterial blood pressure and a chemical control of the peripheral cerebral vessels are of primary importance. Nervous control of vessels in the pia mater is probably useful only for finer adjustments.

The balance between capillary pressure and colloid osmotic pressure within the cranium is one between the colloid osmotic pressure of the plasma (some 26 mm.) and the *difference* in pressure between that of the capillaries and the cerebrospinal fluid (or tissue pressure). Since the latter is of the order of 7 to 10 mm. Hg, the capillary pressure is probably 33 to 36 mm. Hg. A rise in capillary pressure, if associated with an equivalent rise in tissue pressure, would not cause any upset of fluid balance, and a rise in cerebrospinal fluid pressure would tend to accompany and balance any increase in capillary pressure because of the rigid box in which the system is contained. In the erect position gravity would not seriously distort the balance between capillary and tissue pressure. In this posture gravity, acting on the cerebrospinal fluid, raises the pressure in the lower part of the spinal canal, and lowers it within the cranium. Since similar effects are produced in the arterial and venous systems, gravity does not alter the capillary-tissue-fluid balance in an organ immersed in fluid in this way, for the condition is analogous to that of a limb in water (see page 454). Proper venous return from the brain does not, therefore, require valves. Indeed they would be a disadvantage. Like the veins in the peritoneal cavity, those in the cranium and spinal canal do not contain valves.

CHAPTER XXXVII

BLOOD VOLUME IN RELATION TO THE CIRCULATION

It is obvious that the volume of the blood and of the vascular bed must always be identical. The elastic system of vessels may be distended at greater or less pressure, or may even be collapsed, but no vacuum can exist, nor can the system be filled in life with anything but blood. When the blood volume is not adequate properly to distend the vascular bed, the filling of the veins suffers. This is dependent on the activity of the heart in emptying blood from the veins into the arteries. When venous filling is so reduced that the venous pressure is insufficient to fill the heart in diastole, the circulation rapidly fails. With failure of cardiac output there arises an abnormally high permeability in the capillaries as the result of oxygen lack. This increased permeability allows plasma protein to escape from the capillaries. The mechanism for maintenance of blood volume is lost. Progress downhill along this "vicious circle" rapidly leads to death. With the possibility of such a serious sequence of events, it is not surprising that extremely powerful reflex and other adjustments exist to prevent its development.

As has been already explained (page 296) the volume of the blood is determined by the volume of the cells and of the plasma. The volume of the latter is automatically partially regulated by the colloid osmotic pressure of the plasma proteins which causes the passage of water and salts into the blood stream, when the capillary pressure is lowered. This movement of water and salts, however, lowers the colloid osmotic pressure of blood, so that this method of adjustment is limited by the quantity of plasma proteins available. Formation of additional plasma protein can be induced, but it is not a rapid process. The volume of the circulating cells is even less readily altered than that of the plasma, except for such cells as may be stored in the spleen or other reservoirs. Acute changes in blood volume are not readily attained except within certain limits (probably ± 10 per cent).

The discussion of circulatory adjustments already given should have made it clear that relatively enormous alterations develop in the volume of blood contained in the vessels supplying any one area. One is therefore forced to conclude that reflex adjustments must ensure that any changes in one area are at least approximately balanced by equal and opposite changes in another. In other words, the combination of extrinsic with intrinsic vascular reflexes must regulate not only the mutual relationships of blood flow in different organs but also the maintenance of a vascular bed adjusted to the blood volume of the moment. These mutual physiological adjustments of the vascular bed and blood volume play an important part in the compensatory reactions not only to hemorrhage, but also in those to cardiac failure, and they deserve careful consideration.

MUTUAL ADJUSTMENTS OF BLOOD VOLUME AND THE VASCULAR BED

The problems involved in these adjustments, and their importance, may be recognized by considering two types of circulatory failure. In the one, due

to acute and severe hemorrhage, the compensatory adjustments are inadequate, blood volume is reduced, the pressure in the large central veins falls too low, the diastolic filling of the ventricle is subnormal and, following Starling's law of the heart, cardiac output fails. In the other, due to chronic cardiac failure, the heart fails adequately to empty the large veins into the arteries, venous pressure continues to rise, blood volume is increased and again cardiac output fails but with an overdistended, not underdistended, heart. Circulatory failure may therefore be associated with either a low or a high venous pressure.

There are two types of mutual adjustment, or maladjustment, that have to be considered. The one is due to a primary change (reduction or increase) in the volume of the blood to which the vascular bed must be adjusted. The other is due to a primary change in the vascular bed to which the blood volume has to be adapted.

Definitions.—The effects of changes in blood volume on the circulation may be considered as due to *oligemia* (subnormality) or *plethora* (excess). In oligemia the blood volume may be reduced below normal in an absolute sense, or it may be merely subnormal relative to the optimal vascular bed of the moment. Such a relative oligemia is difficult to comprehend, so an example may be cited. A simple hemorrhage gives a temporary absolute oligemia; the vascular bed is reduced proportionately, but such reduction is attained by vasoconstrictions which entail a strain on the system. A general dilatation of the vessels of the skin produced by exposure to heat requires the presence of a large volume of blood in the skin; the vascular bed would be thereby increased, if blood were available to fill the vessels. In any acute reaction the possible change in blood volume is limited in amount, so that the dilatation in the skin can only be attained by constriction elsewhere. This constriction may be sufficient to entail a strain on the system. Though the blood volume has actually not been reduced, but somewhat increased, one may call the condition one of relative oligemia. Changes in blood volume may involve an increase or reduction in both cells and plasma so that normal proportions are maintained; these conditions are known, respectively, as true plethora and true oligemia. Or the proportion of cells to plasma may be altered. If the proportion of red cells is above normal the conditions may be described as polycythemic; if the red cell concentrations are subnormal they may be described as oligocythemic.

Adjustments of the Vascular Bed to Primary Changes in Blood Volume.—The bed is adjusted to the blood volume mainly, if not completely, by reflex mechanisms. The receptors concerned are uncertain; the response to lowered blood volume is one of increased pulse rate and widespread vasoconstriction. Only if the venous return is so poor that arterial pressure falls can these reactions be attributed to reductions in the impulses from the carotid sinus and aortic arch. Often there is an increased pulse rate and evidence of vasoconstriction while the blood pressure is above normal. Since the effects of maladjustment are manifested in inadequate or excessive filling of the large veins it is logical to seek in these areas for the main sensory control. The receptors that cause variations in pulse rate (Bainbridge reflex) and in vasoconstriction (the controversial McDowell reflex) in accordance with venous filling are likely to be concerned. Oligemia, if of mild degree, may be associated with a slowed pulse rate. This is often seen, for instance, in the reaction to a small hemorrhage (see Figs. 209 and 210). Other reactions must be invoked to account for the fast pulse rate that accompanies a marked oligemia. It has

been shown (page 471) that activity of a muscle deprived of its blood supply, so that metabolites collect within it, may induce marked circulatory changes in both pulse rate and blood pressure. It is therefore possible that inadequate venous distention induces vasoconstriction either in the muscles, or in vessels supplying the carotid and aortic bodies. Then secondary reactions might result from such vasoconstriction. Similarly, vasoconstriction in the vessels supplying bone marrow might there lower oxygen tension and start more rapid formation of red cells.

Vasoconstriction or vasodilatation is brought about reflexly and involves large veins, venules, and possibly capillaries. It also includes changes in arterioles in areas in which the circulation can be modified without too great a loss in efficiency. The areas so involved vary with the conditions (see Fig. 192, page 474). If a considerable widespread constriction of arterioles is necessitated for its capacity effect, there may be a rise in arterial pressure due to accompanying increase in resistance as will be seen a little later. Constriction of recognized blood reservoirs also develops. Among these the spleen, the liver with the portal system and also other large veins are probably important. In the dog the spleen certainly contracts forcibly following a reduction of blood volume by hemorrhage. Similar contractions in man have been denied on the basis of the much smaller content of smooth muscle in the human spleen; however, smooth muscle is present and is probably adequate to produce a response.

Chemical factors may be concerned in adjustments of the vascular bed to fit the blood volume. Certainly adrenalin secretion is likely to be exaggerated in response to any considerable strain. Increased secretion has been described following severe hemorrhage and accompanying surgical shock. Both conditions are associated with reduced blood volume and in each, to attain survival, the vascular bed has to be reduced.

Adjustments of Blood Volume to Primary Changes in the Vascular Bed.—If the vascular bed be increased, the blood volume has to follow. Cases in point are the enlarged blood volumes observed to accompany hyperthyroidism (with its active blood supply to muscles for metabolism and to the skin for heat loss) and exposure of the normal subject to heat (active supply to the skin). In such adjustments the blood volume may be changed by alterations in the plasma volume, in the cell volume, or in both.

The Adjustment of Plasma Volume.—This may be attained by altering fluid balance in the capillaries by changes in capillary pressure. Any absorption of fluid into the capillaries lowers the plasma protein concentration, any loss of fluid from the blood raises this concentration. Plasma protein tends to remain only relatively constant in amount. Any lowering of its concentration tends to induce further formation of plasma protein, any increase to induce protein removal. Large changes in plasma protein may require some time (days) but evidence of quite large acute changes in the total circulating plasma protein has been advanced. Possibly there are extravascular reservoirs. The regulation of the colloid osmotic pressure of the plasma is not attained by any simple reversible reaction which maintains a normal concentration of plasma protein. It has been shown that the nonprotein gum acacia, with its own colloid osmotic pressure, reduces the plasma protein level.[328] Colloid osmotic pressure, rather than mere protein concentration, appears to be the thing which is regulated.

Red Cell Formation.—If blood volume changes involve either increases or decreases in plasma volume, the red cell concentration is thereby reduced or increased. Reduction appears to be followed by an increased rate of cell formation and vice versa. Excessive cell concentrations are probably also accompanied by an increased rate of cell destruction. The mechanism regulating the rate of red cell formation is believed to be the supply of oxygen to the bone marrow. Sometimes there is increased red cell formation when the red cell concentration and oxygen saturation of arterial blood are both normal, and when the blood pressure is normal. An involvement of the arteries supplying the bone marrow in a vasoconstriction reaction is a probable explanation.

OLIGEMIA

Conditions of absolute oligemia develop as the result of loss of blood by hemorrhage, loss of fluid by excessive sweating, vomiting, and diuresis, or because of an inadequate supply of fluid. Hemorrhage is associated with absorption of fluid from the tissues and a reduction in red cell and protein concentrations in the blood, dehydration by the opposite effects. Such changes may be considered as normal physiological occurrences, and only as pathological when excessive. Another condition which must be considered is that of surgical shock. In this condition the impermeability of the walls of the capillaries to plasma protein is lost, so that proteins tend to leak out from the capillaries into the tissues. The whole mechanism retaining the blood plasma within the vascular system is thus lost, and the condition, if not rapidly corrected, becomes irreversible. The causation of the change in capillary permeability is uncertain; probably there are many causes, of which oxygen lack is one. Shock may therefore develop as a late stage of hemorrhage, and under these conditions the dilution of the blood with lowered concentration of red blood corpuscles is reversed.

Hemorrhage

The General Picture.—When an animal is bled rapidly from a large artery there is an immediate fall in pressure which is due to the shunting of blood from channels which offer resistance to its flow. When the open vessel is clamped and the resistance restored, the arterial pressures return relatively quickly toward their normal values; if the hemorrhage has not been great the normal mean pressure may be regained or even exceeded. Even after rather severe hemorrhage, despite a very considerable decrease in blood volume, an animal or a patient may show no particular abnormality even in the course of a detailed examination. Nevertheless, the situation may be most critical, for, as we shall see, compensatory mechanisms are in vigorous action, and a small additional strain may lead to their failure.

The course of the changes which occur as a result of a series of successive hemorrhages in an experimental animal are well shown in Figs. 209 and 210 which present data obtained by Meek and Eyster.[238] In some experiments pulse rates, mean blood pressures, cardiac size (measured by the x-ray), and hemoglobin percentages were recorded, while in others maximum and minimum pressures were measured by valved manometers and the cardiac output was determined by a heart plethysmograph with the chest open.

The data of Fig. 209 demonstrate that in a morphinized dog a loss of blood up to 28 Gm. per kg. body weight (or up to 28 per cent of the assumed blood volume) may not cause

any increase in pulse rate, decrease in blood pressure, or change in cardiac filling. Hemoglobin estimations, as well as determinations of the specific gravity of the blood, showed that at this stage not more than 5 per cent of the blood lost had been replaced by absorption of tissue fluid. When the blood loss exceeded 28 Gm. per kg., there was a marked fall of pressure which sometimes progressed even when no further bleeding was induced; there was always a considerable increase in pulse rate and decrease in cardiac volume.

Comparison of Fig. 210 with Fig. 209 shows that in the etherized dog the amount of blood that can be lost without failure is much less than in the unanesthetized animal; when blood loss reached 8 Gm. per kilo, the blood pressures fell because of failure of compensation. Even in the etherized dog a lesser loss (6.7 Gm. per kilo) produced only slight changes, namely, a temporary reduction of venous pressure, and a temporary rise in the arterial pressures with return later of both mean and pulse pressures to slightly subnormal values. The pulse rate change was slight, and the minute volume was only slightly reduced. The further loss of only

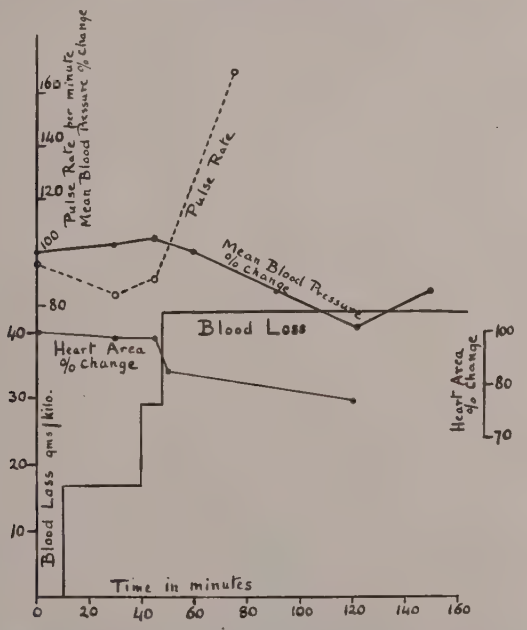


Fig. 209.—Effects of hemorrhage in unanesthetized dog under morphine. Abscissae: time in minutes. Ordinates: pulse rate per minute; per cent change in mean blood pressure; per cent change in heart area determined by x-ray; blood loss in grams per kilo of body weight. (Redrawn from data reported by Meek and Eyster, Am. J. Physiol. 56: 1, 1921).

1.3 Gm. per kilo, therefore, made a great change: the minute volume of blood flow fell from 90 to 35 per cent of the normal value and the pulse rate was much increased; though the pulse pressure and venous pressure were markedly reduced, the arterial pressure actually rose. Further hemorrhage (exceeding 8 Gm. per kilo) had little additional effect on cardiac output or venous pressure but did lower the arterial pressure levels.

These examples indicate clearly the picture of uncomplicated hemorrhage, one which cannot be too firmly impressed on the minds of prospective surgeons. The most striking points, amply confirmed in clinical experience, are the initial maintenance of arterial pressures, pulse pressure, and pulse rate and even of venous pressure, following a hemorrhage, so that the individual shows no par-

ticular abnormality even on the basis of such detailed study. Yet even a small additional hemorrhage may precipitate a crisis, when a normal individual with similar pressures would have withstood a loss five times as great with little or no symptoms. In addition, the person is rendered hypersensitive to other strains, such as those imposed by injury or anesthesia.

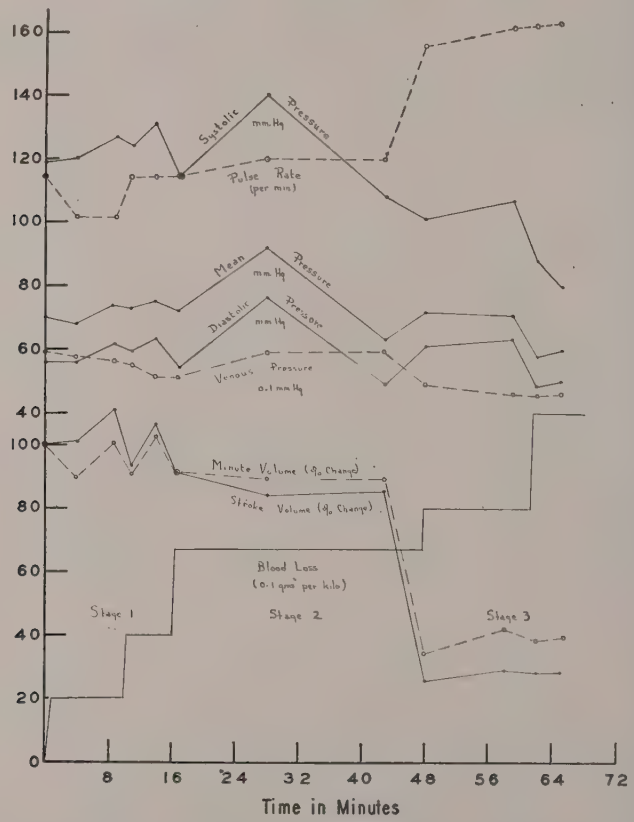


Fig. 210.—Effects of hemorrhage in etherized dogs. Abscissae: time in minutes. Ordinates: blood pressures in mm. Hg; venous pressure in 0.1 mm. Hg; pulse rate in beats per minute; minute volume and stroke volume in percentages of normal values; blood loss in 0.1 Gm. per kg. of body weight. The effective peripheral resistance, calculated from the relation of mean pressure to cardiac output, increased after hemorrhage; it showed ratios to the initial value of 1.04 at fourteen minutes, 1.48 at twenty-eight minutes, 2.43 at fifty-nine minutes, and 2.20 at sixty-five minutes. (From data reported by Meek and Eyster: Am. J. Physiol. 56: 1, 1921.)

Animals or men in *the stage marked 1* in Fig. 210, may have exhausted much of their power of compensation and yet give no indication of this either in blood pressure levels or symptoms. An example[199] in man may be quoted: A blood donor had initially a red cell count of 5.4 million per c. mm., a pulse rate of 60, and blood pressure of 118/78. An hour after giving 880 ml. (13.5 Gm. per kg.) of blood, the cell count was 5 million, the pulse rate 60, and blood pressure 120/80. Although probably less than half of his readjustment had been accomplished by absorption of body fluid which raised the blood volume toward normal (the following day his red cell count had fallen to 4.6 million), compensation had been effected.

In *the stage labelled 2* in Fig. 210 which follows the combination of a moderate hemorrhage with another strain (anesthesia), there may be definite symptoms. This is a stage which is seen in the unanesthetized subject after a larger hemorrhage. In the unanesthetized person the most striking symptom is restlessness. This serves to improve venous return by the muscular pump mechanism and appears to be a reflex phenomenon. If venous return be improved by raising the subject's legs or by intravenous replacement of lost fluid, this restlessness may disappear, even in subjects on whom sedative drugs have little effect. In this stage the sensitivity to further blood loss or other damage is still more marked than in Stage 1, and even a quite small additional hemorrhage may be very serious. Yet there may be little indication of the severity of the subject's condition other than that obtainable from the history. Commonly the pulse rate is raised, but blood pressure may be only a little below, or even above normal. For instance, a patient operated upon for a penetrating head wound lost 760 ml. of blood (12 Gm. per kilo) under ether. This loss, though less than that of the donor already mentioned, was effectively larger owing to the summation of effects from the operation and anesthesia. Before operation the blood had an oxygen capacity of 17 ml. per 100 ml. of blood, the pulse rate was 86 and the blood pressure 122/80. Three-quarters of an hour after the operation (which lasted forty-two minutes) the oxygen capacity was 16.5 ml., the pulse rate 120, and the blood pressure 106/70; twenty-four hours after operation the oxygen capacity was 15.75, the pulse rate 100, and the blood pressure 127/86. Compensation was achieved with little fall in pressure, even though the normal blood volume was only slowly regained. No treatment was required other than rectal administration of saline. The condition, however, was critical and a small additional hemorrhage would no doubt have been serious. The change in pulse rate was almost the only indication of the strain imposed.

In the *stage labelled 3* in Fig. 210 the condition has passed the critical stage and become serious. Even so this fact is not at first clearly indicated by the blood pressure levels. Between stages 2 and 3 the cardiac output was reduced more than 60 per cent (to a level only one-third the normal), yet there were only slight reductions in diastolic pressure (11 per cent), in mean pressure (14 per cent) and in systolic pressure (26 per cent). But there was a considerable increase in the pulse rate (42 per cent) and a reduction in venous pressure (22 per cent). This relatively slight reduction in venous pressure had produced a marked effect on the output of the heart per minute. The greater effect on the stroke volume is usually present and is partly dependent on the increase in pulse rate, but once the ability of the vascular system to effect adjustments by reducing its capacity has become exhausted the reduced output is the necessary sequence of Starling's law of the heart. A similar effect may be demonstrated in Daly's closed circuit heart-lung preparation.[84] The withdrawal of 10 per cent of the blood from the system may lower the cardiac output 20 per cent. The smallness of the change in venous pressure is partly dependent on the lowered cardiac output, which itself tends to raise venous pressure and so to mask the diminished venous return that has induced it.

Compensation for Blood Loss.—The general mechanism of compensation involves two main factors: (a) reduction of the capacity of the circulatory system and (b) replacement of the blood lost.

The principles concerned have already been discussed. The reduction in the capacity of the vascular bed involves reservoirs, such as the spleen, and constriction of large arteries, arterioles, capillaries, venules, and veins. The contraction of both venules and large veins in the skin is readily visible. Contraction of venules and capillaries was demonstrated by Meek and Eyster. Evidence of general contraction of arterioles resulting in an increased resistance is also given by this work. A high effective resistance may be calculated from the relation of mean pressure to cardiac output shown in Fig. 210. Contraction of the large arteries is also indicated by the marked reduction in stroke volume without a proportional reduction in pulse pressure. The vessels must have been less distensible. Direct evidence of such contraction of large arteries has been obtained by Schretzenmayer.[280] More direct evidence of constriction of arterioles may be obtained by separating a vessel from its connection with the aorta and perfusing it at a constant pressure; if the arterioles

constrict, the flow is reduced. Such constriction has been repeatedly demonstrated[24] after hemorrhage. A similar method may be used to show that constriction occurs in the large veins of the mesentery. The importance of the veins in relation to adjustments of the vascular bed is made evident by reference to the large proportion of the blood held in the venous side of the system (see page 341).

In a condition such as that indicated in stage 1 of Fig. 210 constriction of blood reservoirs and some of the large veins together with some fluid absorption probably plays the main role in adjustment. In the second stage arteriolar constriction, utilized for its effect on the capacity of the system rather than on peripheral resistance, begins to be important. In the third stage the constriction is intensified, and fluid absorption becomes more prominent because of lowered hydrostatic pressure in the capillaries. Fluid absorption, however, may cease and fluid loss occur owing to damage to the capillary wall by anoxemia (due to the arteriolar constriction). Proteins are then no longer retained. In this case the simpler effects of hemorrhage pass into those of surgical shock.

Failure of Compensation.—When the compensatory mechanisms prove inadequate, cardiac output becomes very low (stage 3 in Fig. 210) and the arterial pressure is no longer maintained in spite of the peripheral constriction. Damage to the capillary walls from anoxemia may result from the general lowering of the cardiac output, or the effect may be produced from some local reduction in the circulation. In any case an important factor is the constriction of the arterioles. This is utilized to maintain arterial pressure and to ensure an adequate flow of blood through the cerebral and coronary vessels. It also aids venous return to the heart. Any damage to the capillaries may for a short while be reversible; an adequate supply of blood and oxygen can enable the capillaries to recover. Within a relatively short time the changes become irreversible, and it is for this reason that treatment of hemorrhage must not be overdelayed. The effect of the vasoconstriction in generating shock has been demonstrated by Freeman.[131] Sympathectomized animals cannot develop this constriction; part of their compensation is lost and they are consequently not able to withstand as large a hemorrhage as a normal dog. On the other hand, in the absence of arteriolar constriction the capillaries are less readily damaged from anoxemia. Consequently, irreversible damage is less in evidence. Recovery may be achieved in such animals at a late stage by blood transfusion, a procedure which is ineffective in animals with a normal sympathetic nervous system. Though the sympathectomized animals respond better to treatment, they cannot without treatment stand as great a hemorrhage as a normal animal.

One of the most striking characteristics of circulatory failure following hemorrhage is the rapidity of the collapse, once a breakdown occurs. The primary cause of death is circulatory failure, though respiratory failure often supervenes as the result of the poor blood supply to the medulla. Under such conditions respiration fails while a pulse is still in evidence, but none the less the primary cause of death is circulatory.

Principles of Treatment.—The principles of treatment are simple, namely, the replacement of the lost blood by fluid, by fluid containing some colloid with osmotic effects, or by whole blood.[8, 28] There are difficulties in deciding how much ought to be done and when it should be done. Danger arises from failure to act in time. Circulatory failure usually develops slowly as a vicious circle which can only be broken in its earlier stages. If the

hemorrhage is small, replacement of lost blood may be left to the subject's own tissue fluid. The immediate effects of poor venous return may be overcome by a simple intravenous infusion of saline, which allows the circulation to recover temporarily, and allows the body to mobilize some of its defenses. The fluid will not be retained except in so far as the body can mobilize fresh plasma protein. If the saline be given too rapidly so that pulmonary arterial pressures are unduly raised, pulmonary capillary pressure may be raised at the same time that colloid osmotic pressure is reduced. Lung edema may result. Fluid may be given with adequate colloid, either in the form of a solution of gum acacia (some preparations are toxic to man and must be avoided) or in the form of blood plasma (usually citrated plasma is used). If the red cells are also seriously reduced, blood transfusion is obviously indicated. The principles for testing blood incompatibility have already been given (page 302).

Tests for compatibility should always be made except where extreme urgency prohibits them. The time factor may, under certain conditions, dominate all other issues. Where blood transfusion is performed without blood tests, no symptoms are seen in approximately 2 out of 3 cases. Reactions are very rare if the so-called "universal donors" (Group O) are used for all cases.

Oligemia Through Fluid Loss

Symptoms very akin to those of hemorrhage are observed with dehydration. For instance, they occur in hyperpyrexia with pronounced sweating, *if fluid intake is prevented.* Here a very considerable water loss occurs; since much of it comes from the tissues, it does not greatly diminish blood volume. But the same general picture may be produced with fluid losses of 30 to 60 Gm. per kg. of body weight if the condition is combined with widespread vasodilatation of the skin from exposure to heat. Under such conditions changes in hemoglobin suggest a 10 to 15 per cent reduction in blood volume. When the heat is discontinued, and the skin vessels are allowed to constrict, all marked symptoms disappear. If the heat is continued during the dehydration, the conditions resemble those that follow moderately severe hemorrhage: the cardiac output is reduced, the pulse rate is increased, the blood pressures (mean, systolic, and diastolic) are at first often increased, and restlessness is a prominent symptom. If the exposure is carried further the more critical effects that accompany severe hemorrhage may develop.

Other causes of fluid loss may give similar changes. The dehydration accompanying violent diarrhea may give rise to some of these symptoms. In the case of extensive burns it is probable that the marked loss of fluid by evaporation from the surface, accompanied, as it is, by the loss of considerable amounts of plasma proteins, accounts for many of the symptoms.

Traumatic Shock

Surgical or traumatic shock may be defined as a condition of progressive circulatory failure induced by trauma in which the blood volume is inadequate. The blood volume is usually reduced in the absolute sense; it is always subnormal relative to the optimal capacity of the vascular bed at the moment. Many factors can contribute to the production of shock. In the variety of its causes and its final uniformity it may be compared to death itself. One cause of shock has already been noted, namely, hemorrhage. The low blood flow may so damage capillary walls that they become permeable to protein, so that the normal safeguards are lost. The simpler reaction to hemorrhage then develops into the vicious circle of shock, as the blood volume is progressively reduced. This development is characteristic of the ultimate stages of shock. The various types of shock merely designate the circumstances which may lead to this change in the capillary wall. Shock may develop almost instantly at the time of injury, and it is then known as *primary shock;* it may develop slowly after some hours and is then known as *secondary shock.*

Primary Traumatic Shock.—In the case of an excitable subject even mild injuries may be followed by loss of consciousness, sweating, slow pulse, and low blood pressure. This fainting reaction soon passes away and leaves noth-

ing more serious than a sense of exhaustion. A similar but more intense immediate reaction to severe injury may develop in any subject. An excitable temperament is not necessarily involved. The reaction appears to be reflex in character. The vascular changes are such as to decrease, or even to prevent, hemorrhage from severe lesions.

An example of such shock is the following: A boy of nineteen, while lying in a shallow trench, was hit by a shell fragment and suffered a compound fracture of the tibia and fibula; he did not lose consciousness. There was no appreciable hemorrhage. Two minutes later his chief complaint was thirst; he had no pain. He was extremely restless, throwing the injured leg about with flail-like motions at the fracture. Although sweating profusely he complained of feeling cold. Respiration was apparently normal. The pulse was at first slow, later became rapid, and remained small and barely palpable. On the basis of findings in similar cases his systolic pressure was probably below 70 mm. Mentally he was quite alert and talked about his experiences while the limb was splinted without anesthesia; apparently this procedure gave him no pain. Later, his condition improved and he was able to be moved to a dressing station. Descriptions of similar cases, examined, however, longer after wounding, are given by Cowell.[77] The slow pulse and low blood pressure lower the risk of hemorrhage and may prevent it, as in this case and in the following example. A man suffered amputation of a leg and other injuries when run over by a train. No hemorrhage occurred. An hour later the pulse was 80, the blood pressure 60/40. Veins were so contracted as to be invisible, and dissection was required for venous infusion. During the dissection the patient was mentally alert, talked about his home and was not even conscious of the incision, although it was carried out without anesthesia. Thirst, sweating, restlessness, and vomiting were the main symptoms.

The theory that shock is of nervous origin was originally advanced by Meltzer. It appears to be the only satisfactory explanation of primary shock of sudden occurrence which is akin to simple fainting. In both conditions the pulse is slow, cardiac output is probably greatly reduced, and blood pressure is low. Cold sweats and extreme pallor of the skin are seen in both. Primary shock, however, is not necessarily attended by loss of consciousness. Reactions of this type may be considered reflex changes which are adapted to decrease hemorrhage when injury is sustained. The exact mechanisms whereby these changes are effected are not known. Very similar reactions may be produced in animals by excitation of slowly conducting afferent nerves belonging to the C group (see page 471). These fibers are much more resistant to lack of oxygen than are the larger more rapidly conducting axons. Accordingly, if the circulation of a limb is occluded by compression for fifteen minutes or more the C fibers may be the only ones capable of conducting impulses. Under these conditions central stimulation of a nerve trunk gives reflex effects which are due solely to the central action of impulses in the fibers of smallest diameter.[69] The responses observed in the anesthetized animal are increased respiration and a profound fall in arterial pressure which long outlasts the period of stimulation.

Experiments on man demonstrate that reactions of this fainting type may be produced reflexly and are not always emotional in origin. The deep fasciae and also the peripheral arteries appear to be richly supplied with pain fibers of the slowly conducting type, and injury to these structures produces a dull, very unpleasant pain, often associated with reflex responses similar to those just described. Thus a needle may be introduced through the skin of the thigh and moved about in the subcutaneous tissue for fifteen minutes or more with little or no reaction, yet, if it be thrust into the fascia lata and moved about, a fainting reaction with cold sweat, pallor, slow pulse, a desire to vomit and perhaps diarrhea may be induced within a minute. Such reactions closely resemble

those seen in primary shock. Since the C fibers are relatively resistant to anoxemia, impulses from their receptors might come to dominate the situation more and more as the circulation failed. Involvement of such fibers would also help to explain the fact that it is the dull type rather than the acute type of pain which is associated with shock.

Shock of this type would appear to depend on a reduced cardiac output of reflex origin. The reflex might be protective in character, and yet, if extreme, induce its own dangers. The blood volume would initially be reduced only relatively; some part of the vascular bed must be so dilated that the distention of the central veins is subnormal. Nothing is known as to the vessels concerned in such dilatation. The superficial vessels of all types appear constricted. If the subnormal circulation is long maintained, damage to the capillary walls develops, a progressive reduction in the absolute blood volume is induced, and shock, in the more specific sense of the term, follows.

Secondary Shock and Postoperative Shock.—An example of secondary shock given by Cowell[77] is that of a man with one leg blown away below the knee, who shortly after being wounded had a pulse rate of 96 and a blood pressure of 112/70. Five hours later the blood pressure had fallen to 88/62. In secondary shock the pulse rate is usually rapid, in strong contrast to the condition of primary shock. Postoperative shock is similar. Usually there is a history of a critical condition at some stage in the operation. The intervening period of some hours, when the circulation appears to be in fair condition, is presumably associated with reflex compensatory adjustments similar to those noted following hemorrhage. These adjustments mask the seriousness of the situation, and, if they fail, the condition rapidly becomes critical.

Thus in the development of secondary shock there is a latent period during which the circulation appears to be almost normal. The pulse is fast, the pulse pressure perhaps somewhat reduced, but there is little other indication of abnormality. The shape of the pulse, however, is abnormal. There is usually evidence of leakage of fluid from the vascular bed in an increased concentration of red blood cells. Measurements of plasma volume by dye injection (Keith[199]) demonstrate that this increased concentration of cells is caused by loss of plasma fluid from the vascular bed. This reduction in plasma volume may be present even when no concentration of red blood cells is observed; if an earlier hemorrhage has reduced the red cell concentration, any later increase will not be recognized.

The Nature of Shock.—In experimental shock the peripheral arterioles are constricted. If an artery be perfused from a reservoir, it is found that the resistance to perfusion is increasing when shock develops. This constriction is mainly of nervous origin, as was demonstrated in the experiments of Seelig and Joseph.[282] They cut the cervical sympathetic on one side in a rabbit and after producing experimental shock raised the blood pressure in the head by constricting the aorta. The vessels of the denervated ear were widely distended; those on the innervated ear remained constricted.

As already pointed out blood volume is reduced but plasma volume in particular is low; the proportion of cells to plasma is increased. This cell concentration is not necessarily present when hemorrhage complicates the picture, for then there may be an initial dilution which is later followed by concentration. The diminution in blood volume may be demonstrated in experimental shock, whether produced by exposure of the gut or by histamine. For example,

Mann[228] found that normally 76 per cent of the blood can be obtained from the large vessels of a dog at death, but that in an animal shocked by peritoneal exposure only 39 per cent can be recovered.

It is apparent that shock is circulatory failure, in which the volume of blood in circulation is diminished, the arterial pressure usually lowered, and cardiac output diminished. The change in blood volume may be augmented by hemorrhage or sweating, but it can be entirely the result of displacement of fluid within the body. A loss of circulating blood may result from vasodilatation. The expanded vascular bed traps large quantities of blood which are relatively static. In this case there may be no loss of plasma; more commonly, however, especially in postoperative shock complicated by anesthesia, a differential loss of plasma occurs, and the corpuscles are concentrated. The arteriolar portion of the vascular system is not the site of the vasodilatation, for the peripheral resistance is increased, and in the skin constriction appears to involve both capillaries and venules. In other areas the capillaries or perhaps veins may be widely dilated.

It is not always easy to distinguish the development of shock, or to determine the effectiveness of any treatment applied. Two simple physiological methods of measurement appear valuable. The measurement of the specific gravity of either whole blood or plasma by the falling drop method presents a rapid and simple method for following hemoconcentration with quantities of blood such as may be obtained from a finger or an ear. An additional indication of conditions liable to lead to shock may be obtained by simple surface temperature measurements. Ipsen[187] has utilized this method and finds that a simple flat mercury thermometer strapped by adhesive to the sole of the foot is adequate. Patients who are normal operative risks show a rapid rise in the skin temperature of the sole of the foot on induction of general anesthesia. This rise in temperature is absent or evanescent in patients who are bad surgical risks because of threatening shock. The probable explanation is simple. The normal subject maintains vasoconstriction in the skin as part of the mechanism of temperature control. Anesthesia interferes with the hypothalamic temperature regulating centers, and the vasoconstriction disappears. If, however, the subject is dehydrated and vasoconstriction is present as a reflex adjustment to lowered blood volume, the reflex constriction is probably mediated through centers in the medulla. These are not readily depressed by anesthesia, so that no rise of temperature occurs. The absence of such a rise indicates an extremely strained vascular system and warns that insults from anesthesia or operation should be reduced to a minimum.

Causation of Shock.—Analysis of the causation of shock depends mainly on the experimental production of shock or of shocklike conditions. Two of these have already been mentioned. The intense vasoconstriction that results reflexly in the adjustment to hemorrhage may lead to capillary damage and development of shock. A profound reflex fall of blood pressure may result from stimulation of C fibers, which mediate pain. This is perhaps a factor inducing capillary damage. The third possibility suggested, namely the toxic effect of some substance with actions similar to those of histamine, deserves further consideration.

Intravenous injection of *histamine* can cause rapid circulatory failure with many of the symptoms of shock.[80, 83] The blood pressure falls. In many species the arterioles appear to be constricted while the capillaries are dilated and

become permeable to the plasma proteins. Increase in the percentage of hemoglobin indicates a marked reduction in blood volume which is inadequate to fill the expanded vascular system. Venous return is impaired, and though the heart continues to contract forcibly for a while, it is inadequately filled and the contractions are ineffective. The susceptibility of an animal to the effects of histamine is exaggerated by a contemporaneous or even a previous hemorrhage and by chloroform and ether but not by nitrous oxide-oxygen anesthesia.

Symptoms similar to traumatic shock may accompany the anaphylactic responses to foreign proteins which occur in sensitized animals. Such responses vary greatly in different animals but in some give a picture of circulatory collapse. There is evidence that histamine-like substances are liberated locally, particularly in the bronchial type of response in guinea pigs.[87]

It is possible that substances identical with, or similar to, those which contribute to the development of inflammatory responses are liberated in shock. If such responses were widespread, or if chemical factors responsible for them escaped into the general circulation a shocklike condition might be expected to develop. Data obtained on patients following operation indicate a subnormal level of blood histamine (Rose and Browne[265]). This need not cause abandonment of the theory, for there may be transfer of histamine from the blood to certain of the tissues. Experimental evidence in support of such a toxic origin of secondary shock was secured by Bayliss and Cannon.[62] They found that traumatization of the thigh muscles in the anesthetized cat causes, after some delay, a condition which closely resembles secondary shock. In their experiments extravasation of blood in the injured region seemed insufficient to cause the symptoms. Reflex and other nervous effects were ruled out as essential factors in determining the result by the finding that after section of all nerves to the limb traumatization led to the development of a condition quite similar to that obtained when the nerves were intact. In other experiments they found that previous ligation of the blood vessels of the leg prevented the shocklike effects of crushing the thigh muscles. From these and other experiments they drew the inference that a pressure-lowering material is given off to the blood from injured tissue, "is carried to the rest of the body, proves toxic and disturbs the vessel walls or their control in such a way as to lower arterial pressure." Experiments by O'Shaughnessy and Slome[244] have thrown some doubt on the simple histamine hypothesis. They found that blood from an animal in shock produces a pressor response when injected into another animal, while blood from an animal injected with histamine produces a depressor reaction. In another type of experiment the leg of a dog was entirely disconnected from the body except for the nerve supply; its blood vessels were connected with the circulation of a second dog. When the leg was injured both animals developed shock. The result shows, of course, that both nervous and humoral factors were involved, but it is difficult to be certain that in these experiments on anesthetized animals the shock produced by the nervous response was fundamentally the same as that evoked through the humoral change.

A factor of considerable importance in the development of shock, particularly in the production of experimental shock under anesthesia, is the loss of fluid into the traumatized tissues. This loss includes both blood plasma and cells, but the loss of plasma usually exceeds that of cells. A similar loss of

plasma occurs in the exudates from burns and contributes largely to the development of shock in such conditions. This side of the subject is discussed in the recent book by Blalock.* While such losses undoubtedly constitute an important contributory factor in the genesis of shock, they are unlikely to be the main factor, at least in the unanesthetized human subject. One may see cases without severe shock, in which there is severe injury involving bones and muscle tissue with extravasations of large volumes of fluid measurable in liters. One may also see cases in which shock is profound, although there is little extravasation of fluid and negligible external blood loss.

Certainly many other factors may be concerned in the genesis of shock, since anything which tends to damage the capillary wall will contribute to development of shock. Anesthesia is itself a big factor, particularly the more toxic volatile anesthetics such as chloroform and ether. Nitrous oxide anesthesia appears to be much less toxic in this respect, provided that sufficient oxygen is given to prevent anoxemia. It was originally shown by Yandell Henderson[164] that, if a light ether anesthesia was given, hyperpneic responses to pain or to the irritating effects of ether itself developed, and led to lowered carbon dioxide concentrations in the blood. This condition is called acapnia. It involves the replacement of a CO_2 stimulus to respiration by one of oxygen lack, and is associated with irregular or periodic breathing. The resulting anoxemia must naturally contribute to capillary damage. though the capillary damage thus caused is probably rarely the direct cause of shock, it is often a contributing factor, and one which should always be considered in the administration of anesthetics. However, the anoxemia that develops secondarily from overventilation in light anesthesia is not nearly so dangerous as the more marked and continuous anoxemia that results from depression of the respiratory center by excessive anesthesia. The latter is a still greater contributing cause of shock.

It has been emphasized by Yandell Henderson[165] that voluntary *hyperpnea* in man may cause a fall of venous pressure, occasionally accompanied by some decrease in arterial pressure, and associated with marked pallor of the skin, sweating, a small thready pulse, and lack of sensation of pain. The condition resembles shock. He has shown that hyperventilation can cause circulatory failure in animals and this has been confirmed[82] (see page 476). On these grounds he advanced the theory that *acapnia* (loss of CO_2 from the blood) is *the cause* of surgical shock. Some of his data may be briefly cited. Dogs anesthetized with ether in such a way as to leave their respiration as normal as possible were in good condition after six hours; others only lightly anesthetized showed the excessive ventilation which accompanies hyperexcitability and were moribund within five and a half hours, in spite of the smaller dose of ether. Animals with respiration depressed by excessive ether died within two hours. On the other hand, dogs maintained under light anesthesia, though showing excessive ventilation, remained in excellent condition for six hours, if they were made to breathe a mixture of 7 per cent carbon dioxide in oxygen. Both the CO_2 content and capacity of the blood were reduced in the lightly anesthetized dogs breathing normal air, but not in deeper types of anesthesia.

If a high arterial pressure is maintained for some time in a normal animal by slow intravenous injection of adrenalin, a profound fall of blood pressure with concentration of the blood may result when the injection is stopped.[19] The condition closely resembles shock. This may be interpreted as the result of continued anoxia of the capillaries produced by vasoconstriction. When capillary flow and pressure are restored, the endothelium is permeable to protein.

*A. Blalock: Principles of Surgical Care, The C. V. Mosby Co., 1940.

Exhaustion of the adrenal glands may occasionally be a factor in the development of shock, but any exhaustion theory seems incapable of explaining shock entirely. When the adrenal glands are removed, animals may show a profound fall in blood pressure, an incapacity to compensate by dilution of their blood by tissue fluid absorption, and the development of a shocklike state. When injected with *cortin* such animals regain a normal condition, if the shocklike state has not been too prolonged. It has long been known that adrenalectomy renders animals profoundly susceptible to histamine injection, injury, and hemorrhage, so that operative procedures may be fatal.[80] This susceptibility is removed by cortin.[293] It is therefore not unlikely that the adrenal cortex is of importance in the mechanisms concerned with the compensatory reactions which occur in such emergencies. But since removal of all adrenal cortical tissues does not lead to shocklike symptoms for several days, it does not seem possible that a deficiency of cortical hormone can be involved in the shock which appears only a few hours after trauma.

One is forced to the conclusion that though the exact genesis of shock is obscure, it is most unlikely that this condition has a single cause. It represents more probably a whole group of circulatory failures of somewhat different origins, but all characterized by an acute oligemia.

Principles of the Treatment of Shock.—The physiological principles involved in the treatment of shock depend, as in hemorrhage, on the restoration of a more normal blood volume, and the restoration of a normal capillary wall. As in hemorrhage time is an important consideration, for changes rapidly progress until they are irreversible. Fluid to increase blood volume preferably containing some substance of high colloidal osmotic pressure is obviously indicated. Gum acacia solutions are valuable, but plasma or whole blood is better.[43] Plasma not only restores the colloid osmotic pressure (if a permanent leakiness of the capillaries has not been induced) but also supplies needed protein materials and often useful antibodies. It can now be stored sterile and dry in the so-called lyophile state (dried at extremely low temperatures).

The experimental production of shock by adrenalin infusion serves as a warning that measurements of arterial pressure alone are not an adequate guide to the condition of the circulation. Though adrenalin may be useful as a temporary measure to restore a failing coronary circulation, it is obviously not indicated as a general antidote to shock. It should be employed with circumspection. Toxic substances such as chloroform and ether, as well as anoxemia from any cause should all be avoided. The principles involved in the causation of shock are of importance in developing treatment so that shock may be avoided. Shock when fully developed is very difficult to treat. Particular care should be taken to prevent unnecessary dehydration. Above all it is important to remember that the initial stages of shock are often not evident. Compensating factors are active as they are after hemorrhage, and a threatening collapse may develop with little warning. The margin between a compensated and uncompensated change is very small.

PLETHORA

The reductions in blood volume that have already been discussed are primary changes to which the cardiovascular bed is adjusted. Primary increases in blood volume may be produced experimentally, but are rare both physiologically and clinically. On the other hand, primary increases in the vascular bed to which the blood volume has to be adjusted are common. A very important instance is the large increase in volume that accompanies the cardiovascular adjustment to cardiac decompensation. In discussing plethora one must consider its experimental production, the physiological adjustments it provokes and the relation of both of these to the conditions accompanying cardiac failure.

Hydremic Plethora.—When an animal or man is infused intravenously with saline, a condition of increased blood volume is induced. A diffusible substance, such as NaCl or glucose, thus injected, dilutes the blood and lowers the colloid osmotic pressure. At the same time the increased volume tends to raise venous pressure, to increase cardiac output, and secondarily to increase arterial pressure. A raised capillary pressure results, which, added to the lowered colloid osmotic pressure, helps to filter the fluid from the blood into the tissues. The blood volume therefore soon returns to normal. If the solution be injected in a hypertonic strength, it can temporarily attract fluid from the tissues, but the other changes are merely somewhat postponed. If the solution injected contains some colloid which is retained by the capillary wall, whether this be plasma protein or some substance such as gum acacia, the fluid is retained with it. The volume then returns to normal only as the total colloid is reduced by removal of the plasma protein or gum acacia.

When a saline or glucose infusion is given rapidly by vein a marked rise in venous pressure may result, even if plethora is not induced. This may distend the heart beyond the range of physiological advantage, and so lead to cardiac embarrassment. Another possibility is that by raising pulmonary pressure at the same time that it lowers colloid osmotic pressure, the infusion may cause pulmonary edema. Such results may be avoided if the fluid is given slowly, and particularly if it be given through a leg vein. It should always be remembered that between the veins of the leg and the heart is the venous reservoir of the inferior caval system (and its hepatic branches) which can act as a buffer.

True Plethora.—If blood be injected intravenously, the blood is increased in volume without at first any change in composition. The classical description of such conditions we owe to Starling.[286] Starling injected large volumes of defibrinated blood into dogs. He noted the dilatation of vessels that allowed this blood to be accommodated and found that the greater part was stored in the large veins. The blood was concentrated by removal of fluid, which he attributed to the raised capillary pressure. The consequent concentration of corpuscles left a highly viscous blood, which the heart might be unable to expel. He noted that death might result, preceded by a high venous pressure and a grossly overdistended heart. The animal could be saved by venesection which relieved the overdistention and at the same time removed some of the excess corpuscles. Plethora may be induced in man by a blood transfusion,[238] but the injections of blood normally given to anemic subjects do not produce hypernormal concentrations of corpuscles. In these cases the injections are much smaller than the experimental ones described by Starling.

The condition in plethora is in most respects the opposite of that produced by a moderate hemorrhage. Arterial pressure tends to be raised. Venous pressure is raised, and, probably as a result of this change the pulse rate becomes more rapid (Bainbridge reflex) and some reflex vasodilatation may be induced (McDowall reflex). At the same time the rise in arterial pressure, acting through the buffer nerves causes a peripheral dilatation of large vessels, dilatation of blood reservoirs (including skin capillaries and venules), and, if necessary, dilatation of arterioles. The sum total of these effects is to minimize the rise in arterial pressure in spite of the increase in cardiac output which results from a faster heart and a larger stroke volume.

The course of a plethora resulting from transfusion of blood may be illustrated by an actual case. The patient was suffering from anemia and presumably had a normal blood volume. The oxygen capacity of his blood was low, 4.5 ml. per 100 ml. The pulse rate was 120 and arterial pressures 115/70. During transfusion of 500 ml. of blood he showed a slight increase in pulse rate. An hour later the rate had fallen to 108 and the blood pressure was 128/68. The next day the pulse was 104, the arterial pressures 128/75, and the oxygen capacity 7.1 ml. Five days after the transfusion the hemoglobin percentage had risen and the oxygen capacity was up to 8.6 ml.; the pulse had fallen to 84 and the blood pressure to 122/72. These changes suggest that cardiovascular adjustments had accommodated the increased blood volume almost at once (within the first hour), but that a normal volume was regained more slowly (increasing the hemoglobin percentage). When transfusion is carried out after a severe hemorrhage the conditions are altogether different: the added blood is usually inadequate to replace more than a part of the blood lost and the patient, assisted over the initial emergency, continues to increase his volume to normal at the expense of a decrease in hemoglobin percentage.

Physiological Plethora.—An increased blood volume may develop if the vascular bed is enlarged. This is the case in hyperthyroidism. A similar moderate increase may result from the exposure of a normal subject to a hot climate. A large amount of blood has then to flow through the skin and be accommodated in the superficial veins for effective cooling. The reaction of the individual may be described as that to a hemorrhage into his own superficial veins. The adjustment is attained gradually. Presumably blood passes to the dilated veins, and compensation is attained by vasoconstriction elsewhere, including the splanchnic system. The arteriolar constriction lowers capillary pressure and assists absorption of extra fluid from the gut, with lowering of the colloid osmotic pressure of the plasma. Additional formation of plasma protein is thus induced, and the total circulating plasma protein and the plasma volume are both increased. Arteriolar constriction may also involve the vessels to the bone marrow, for increased formation of red cells may commence within a day or two. Ultimately the vasodilatation can be substained without the strain of central vasoconstriction, since an enlarged blood volume of normal composition has been built up.

BLOOD VOLUME AND THE CIRCULATION IN CARDIAC DECOMPENSATION

Cardiac decompensation, a condition resulting from the gradual failure of a diseased heart, is associated with an enlarged blood volume. Recent measurements indicate blood volumes which may be more than double the normal value. That the blood volume is enlarged has been known for many years; it was observed clinically by Lorrain Smith in 1909, and Bolton[42] demonstrated its occurrence as a result of experimental interference with the circulation by constriction of the venae cavae. Even before its occurrence was demonstrated, Starling postulated its development on theoretical grounds. The condition is one of plethora, yet Starling postulated its development as a process related to hemorrhage.[286]

The failing heart is unable to carry its load without utilizing its reserve forces. These are mobilized by its failure to empty adequately the large veins. Venous engorgement develops, and the increased venous pressure acting through Starling's law of the heart allows the work to be accomplished. The engorgement of the central veins utilizes blood which is made available by arteriolar

constriction. The individual was regarded by Starling as having bled into his own large central veins. The reactions to hemorrhage, namely, vasoconstriction, fluid absorption, lowered concentration of plasma protein, new formation of plasma protein, formation of new red corpuscles, follow. In this way the blood volume is increased, and the composition of the blood remains approximately normal. With such reactions the arterial pressure is not reduced, the arterioles may be constricted, and the work the damaged heart has to do remains high. If the load be still further increased by greater activity of the individual, these mechanisms of adjustment are utilized again and again until ultimately the optimal distention of the heart is surpassed. Even when this has happened, these powerful reflex mechanisms, which respond to cardiac failure by evoking reactions designed to raise venous pressure, continue to function. No longer are they advantageous; they have now become a liability. The compensatory reactions increasing blood volume produce a pathological plethora and an overdistended pathologically dilated heart. At this stage venesection reduces the strain just as it relieves an experimentally produced plethora.

The changes in cardiac decompensation therefore start as those evoked by hemorrhage and may end as those associated with plethora. Reflex adjustments which lead to the utilization of Starling's law of the heart are involved. These adjustments are normally advantageous, but conditions may develop when they are not only inappropriate but definitely disadvantageous. The origin of these reflexes is difficult to understand. They can hardly arise from lack of distention of the large veins and auricles, for these are overdistended. The carotid sinus and aortic arch cannot be invoked, for commonly arterial pressures are approximately normal. It suffices to point out that any adequate analysis of the reflex adjustments to hemorrhage will also give an explanation of this sequence of events.

The description given has considered only the period of adjustment, which precedes actual failure. In later stages the high venous pressure, exaggerated by inadequate cardiac output, may raise capillary hydrostatic pressure above the colloid osmotic pressure of the blood. This results in abnormalities of fluid balance, particularly in the more dependent parts of the body where gravity effects aggravate the rise in capillary pressure. Tissue fluid collects more rapidly than it can be drained by lymphatics, and the area becomes edematous. The rise in tissue fluid pressure that results from the edema temporarily counterbalances the increased capillary pressure so that fluid collects more slowly. Gradually the tissues stretch, until they may become waterlogged with large volumes of fluid.

PLETHORAS IN OTHER CLINICAL CONDITIONS

The blood volume may be increased in other clinical conditions, but the physiological principles are less clearly established. An enlarged blood volume is found in the cyanotic varieties of congenital heart disease. Here the heart is partially short-circuited so that some of the blood misses the pulmonary circuit. The resulting anoxemia is probably to blame for the increase in blood volume which involves only the volume of red blood corpuscles and is usually associated with a reduction in plasma volume.[154]

A primary increase in blood volume appears to be involved in polycythemia vera. Here the cells are enormously increased both in total quantity and in concentration and the blood is highly viscous. The great adaptability of the circulation, at any rate in young subjects, is illustrated by the fact that frequently such subjects have perfectly normal blood pressures. The increased resistance produced by the high viscosity is then overcome by vascular relaxation. The condition is considered to be induced by partial obstruction of the blood supply to the bone marrow.

PART IV

THE RESPIRATION

By Carl F. Schmidt

CHAPTER XXXVIII

THE MECHANICS OF RESPIRATION

Foreword.—Respiration may be defined as the aggregate of the various processes involved in satisfying the needs of a living organism for oxygen. Since carbon dioxide is usually removed simultaneously by the same processes, respiration can also be defined as the gas exchange between a living organism and its environment. In air-breathing animals respiration serves the additional purpose of eliminating some of the heat resulting from metabolic activities, particularly muscular contraction, but this function, although very important in some animals (especially in birds and flying insects[94]) is only incidental and subsidiary in man.

Of all the factors concerned in maintaining the normal functioning of a living organism respiration is probably the most essential. Every manifestation of life requires the liberation and utilization of free energy; increased functional activity necessarily entails a commensurate increase in the amount of energy required, and if the supply of energy is insufficient to meet the demand, any living system soon becomes incapable of functioning. In a system doing measurable mechanical work (such as a contracting muscle or a secreting gland) there are obvious reasons for such a relation, but in other structures (such as nerve cells) which do not contract, move, divide, grow, or do measurable work in removing substances from the blood, there is the same requirement for energy in proportion to the intensity of functional activity although here the reason for such a relationship is not so obvious. We shall take up this question later (page 562) and attempt an explanation. The reason for alluding to it at this time is that the energy required by a living cell is derived from chemical reactions occurring within it and, with the exception of those forms that can exist anaerobically, these reactions are oxidative in nature. It follows that an adequate supply of oxygen is a fundamental requirement of all living cells excepting anaerobic organisms. Different forms of life secure their oxygen in different ways; in small marine forms simple diffusion suffices for the gas exchange, but this can be the case only in organisms of small size (less than 0.1 mm. in diameter[94]). Larger forms have developed special apparatus for obtaining and distributing oxygen; in many insects the process is accomplished by piping atmospheric air through small ducts (tracheae) directly to the tissue cells, but in other animals the organs involved in obtaining the oxygen are distinct from those concerned in its distribution. To obtain the relatively enormous amounts of oxygen required by a complex animal such as a vertebrate, special organs have been developed in which an enormous

surface is provided for contact of the distributing medium (blood) with the external environment; in aquatic forms these organs are gills, while in air-breathers they are lungs; in either case the sole function is to make large volumes of the environmental medium available to the organism for its gas exchange, and in order to make this most effective there are muscular movements, suitably synchronized and regulated through the nervous system, by which a rhythmic circulation of the external medium is maintained through the gills or lungs. To transport the gases between the site of the exchange with the environment (external respiration) and the tissues, the distributing medium must be capable of carrying much larger volumes of gases than can be done by simple solution, and this is achieved by another type of specialization, viz., reversible chemical combinations of blood pigments with oxygen and carbon dioxide. The ultimate purpose of the entire series of processes—the uptake of oxygen and elimination of carbon dioxide by the tissues (internal respiration)—is accomplished by diffusion between them and the fluid in which they are immersed, on the one hand, and the blood in the permeable vessels (capillaries) of the circulatory system on the other.

Respiration in an air-breathing animal therefore involves three separate though intimately related sets of processes: (1) *external respiration,* which includes not only the basic function of absorption of oxygen from and excretion of carbon dioxide into the atmospheric air, but also the mechanical (muscular) movements by which the air is made available for the purpose and the nervous mechanisms that preside over the regulation of such movements; (2) *transport of oxygen and carbon dioxide* between the lungs and the tissues, which also includes the physical and chemical processes involved in the transfer of the gases between the blood and the air in the lungs, on the one hand, the tissues on the other; (3) *internal respiration,* which deals with the physical and chemical factors concerned in the uptake and utilization of oxygen and excretion of carbon dioxide on the part of the tissue cells. These sets of processes must be considered separately, but it is well to remember that this is solely for the sake of convenience; actually they are all parts of a coordinated system having only one fundamental purpose, which is to supply the cells of the body with the oxygen they require and to remove the carbon dioxide they produce. This purpose can be frustrated by interference with any of the steps involved with the same end result, namely, decrease in the capacity of the tissues to function, culminating in irreversible changes (death) if the interference is severe and prolonged enough.

THE MECHANICS OF EXTERNAL RESPIRATION

The Respiratory Movements

Movement of air in and out of the lungs is accomplished in all air-breathing animals by the contraction of voluntary muscles. In some animals, such as the frog, air is actually forced into the lungs by a process akin to swallowing. In the higher animals and man the muscular effort is exerted only upon the walls of the thorax, the size of which is alternately increased (inspiration) and decreased (expiration). As a result, the pressure exerted by the thoracic walls upon the pleural surfaces of the lungs becomes alternately lower and higher. The air spaces of the lungs are normally in free communication with the outside air through the respiratory passages, and since the pressure of the outside air

remains constant, air rushes into the lungs when the thorax enlarges and is forced out when the thorax becomes smaller. For the present purpose the part played by the lungs may be regarded as passive, although recent work indicates that this is not strictly true (see page 617).

When all of the respiratory muscles are at rest the thorax assumes the position of passive expiration. Any deviation from this position involves the active contraction of muscles, inspiratory or expiratory as the case may be.

The Movements of the Thorax

The enlargement of the thorax during inspiration is brought about by movements of the ribs, sternum, vertebrae, and diaphragm. The expansion is not equal in all directions, but mainly downward because of contraction of the diaphragm, laterally through elevation of the ribs, and anteriorly because of anterior and upward movement of the sternum. The thoracic wall does not expand at all at the posterior aspect of the apices nor at the vertebral attachment of the ribs (Keith, Macklin).

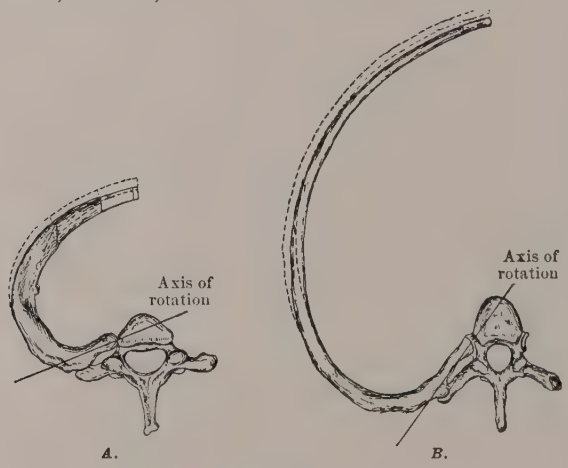


Fig. 211.—*A*, first dorsal vertebra; *B*, sixth dorsal vertebra and rib. Axis of rotation shown in each case.

The Movements of the Ribs.—The first seven pairs of ribs progressively increase in length and are attached to the sternum by cartilaginous bands. The eighth, ninth, and tenth pairs progressively decrease in length and are attached to the sternum by strong cartilage complexes which join the cartilages of the seventh ribs. The eleventh and twelfth ribs have their anterior ends free and may be considered part of the abdominal wall; they play no direct part in respiration.

Each of the first seven pairs of ribs, together with its articulations with the sternum and vertebrae, forms a somewhat flattened ring the plane of which is inclined forward and downward, the inclination increasing progressively from the first rib downward. Consequently any *upward* movement of the ribs increases the anteroposterior diameter of the thorax because it brings the plane of the ribs nearer to a right angle with the vertebral column; the result is to

carry the sternum forward when it moves upward. Since each of the rings formed by the ribs which articulate directly with the sternum has a longer transverse diameter than the one above it, an upward movement of these rings leads to expansion of the upper part of the cavity laterally as well as anteroposteriorly. Another element is *rotation* of the ribs about the axis formed by their attachments to the bodies and transverse processes of the vertebrae (Fig. 211. The double articulation of the rib transforms part of an upward pull into a rotation outward; the shaft of the rib is twisted as it is raised, the torsion being taken up by the costal cartilages. The end-result of all these movements is to increase the anteroposterior and lateral dimensions of the upper part of the thoracic cavity when the ribs are raised. The lower part of the cavity is influenced predominantly by the diaphragm and the enlargement with inspiration is mainly downward; the articulation of the lower ribs (sixth to tenth inclusive) with the vertebrae is such as to cause the lateral and anterior part of each to move forward and outward more than the one above it during inspiration, thus counteracting the inward pull of the costal portion of the diaphragm.

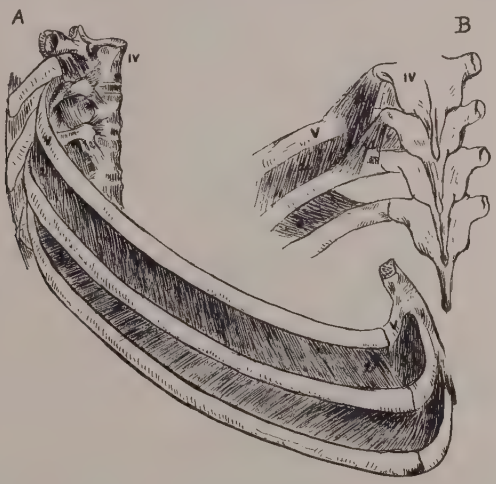


Fig. 212.—Intercostal muscles of 5th and 6th spaces. *A*, side view; *B*, back view; *IV*, 4th dorsal vertebra; *V*, 5th rib and cartilage; *1*, *1*, M. levatores costarum, *2*, *2*, external intercostals; *3*, *3*, internal intercostals, exposed by removal of the external muscles. In *A*, there are no external intercostals in the intercartilaginous spaces; in *B*, there are no intercostals near the vertebral column. (From Allen Thomson.)

In *emphysema,* as well as in deep breathers, such as athletes, the ribs are not further apart but have assumed a position nearer the horizontal than normal (Pancoast, Baetjer, and Dunham[122]). The thoracic cavity is therefore permanently enlarged as it would be by the inspiratory movement of the ribs.

The Action of the Musculature of the Ribs.—Because of the angle at which the ribs are attached to the vertebral column, the progressive increase in the length of the ribs from above downward, and the outward rotation associated with an upward pull, any upward movement of the ribs means an increase (inspiration), and any depression means a diminution (expiration) in the size of the thoracic cavity. The inspiratory muscles therefore are those which run

from the head and neck (scaleni, sternocleidomastoideus) or from the arms (pectoralis minor) to the ribs, and those (intercostales externi) which run from rib to rib in a downward and inward direction (Fig. 212). The levatores costarum and serratus posticus superior, parts of the great mass of muscle attached to the vertebral column posteriorly and running downward from the lower cervical and thoracic vertebrae to the ribs, can also pull the latter upward.

The expiratory muscles are those which run from the pelvis to the sternum (rectus abdominis), or to the ribs posteriorly (iliocostalis lumborum, quadratus lumborum), or from the vertebrae upward to the ribs (serratus posticus inferior); the triangularis sterni runs upward and outward on the inner surface of the thorax from the sternum to the third to sixth ribs, and therefore depresses the ribs; the intercostales interni run downward and outward, almost perpendicularly to the intercostales externi, and contraction of their fibers most probably depresses the ribs. The function of the external and internal intercostals has long been the subject of debate; Bronk and Ferguson[30] have recently studied the action-potentials of the nerves leading into the two muscles in the cat and have found in this way that the muscles are activated alternately, the external intercostals with inspiration, the internal intercostals with expiration.

The respiratory movements of the ribs take place toward two fixed points. The first rib and sternum are elevated directly by the scaleni and sternocleidomastoids and serve as the fixed point toward which the next four pairs of ribs are raised during inspiration; this part of the cavity is conical in shape and the movements of the first five ribs are especially suited to expand the conical upper lobes of the lungs (Keith[92]). The sixth, seventh, eighth, ninth, and tenth ribs are steadied and fixed by the muscles running to them from the pelvis and spine, but the dominant inspiratory influence is the diaphragm (Keith). In expiration the upper ribs move toward the lower, which are pulled down by the muscles which fix them during contraction of the diaphragm; the strongest expiratory influence, however, is contraction of the muscles of the abdominal wall, because of which the abdominal contents are pressed upward against the diaphragm, thus decreasing the vertical diameter of the thoracic cavity.

The Action of the Diaphragm

This dome-shaped sheet of muscle is attached posteriorly to the lumbar vertebrae, laterally to the lower six ribs, and anteriorly to the ensiform cartilage of the sternum (Fig. 213). The fibers sweep upward from these attachments along the inner surface of the ribs, then arch toward the midline to join the central tendon, at which point the pericardium is attached; otherwise the dome is free. When the muscle contracts the dome moves downward and somewhat forward; the thoracic cavity is thus enlarged in the vertical direction and, at its lower end, in the anteroposterior axis as well (Keith). In the process the abdominal viscera are displaced downward and forward and the abdominal wall tends to protrude. For this reason inspiration produced entirely by contraction of the diaphragm is often referred to as abdominal respiration.

The lateral edges of the diaphragm are in contact with the parietal pleura of the thoracic cavity forming what are known as the pleural sinuses. When the muscle contracts these sinuses are opened and the lungs descend in the spaces

so formed. This is accompanied by a slight retraction of the external chest wall which is known as Litten's diaphragm phenomenon. In its contraction the diaphragm behaves like a piston which moves downward and forward, supported by the abdominal contents and creating a space to be filled by expansion of the lungs.

As seen by the x-ray, the dome of the diaphragm is normally higher on the right side than on the left by a distance averaging 15 mm. at full inspiration. The excursion of the domes with inspiration varies greatly among normal individuals, tending to be greatest in athletes and older adults and least in thin women (Pancoast, Baetjer, and Dunham[122]). Keith gives 12.5 mm. as the average inspiratory descent of the whole diaphragm, the right dome moving rather more than the left and the left more than the central part.

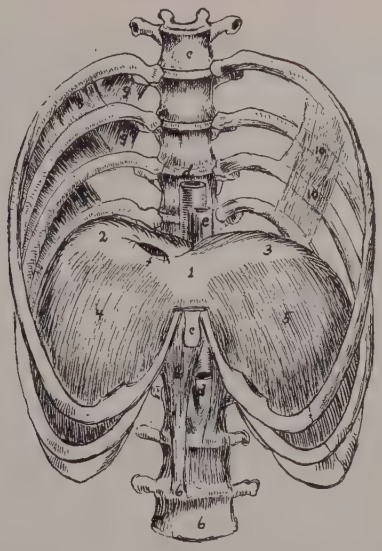


Fig. 213.—Lower half of thorax from the 6th dorsal to the 4th lumbar vertebra, seen from the front. *c*, ensiform process; *d*, *d'*, aorta; *e*, esophagus; *f*, aperture in tendon of diaphragm for passage of vena cava inferior; *1*, *2*, *3*, trilobate expansions of tendinous center of diaphragm; *4*, *5*, costal portions, right and left, of diaphragm muscle; *6*, right crus of diaphragm; *8*, *9*, internal intercostal muscles, which are absent near the vertebral column, where it joins *9* and *9*, the external intercostals; *10*, *10*, subcostal muscles of left side. (From Luschka.)

In natural breathing in the standing or sitting posture there is a *slight extension of the spine* during inspiration. This serves to increase all diameters of the thorax and its absence is undoubtedly an important contributory factor in reducing the vital capacity of an individual when lying on the back. Figures given by Hutchinson for the effect which posture has on the vital capacity are of interest because of their bearing on the cause of orthopnea (see page 650). In the same individual he found the following vital capacities:

Standing	4300 ml.
Sitting	4200 ml.
Supine	3800 ml
Prone	3620 ml.

QUIET AND FORCED BREATHING*

Ordinarily respiration is carried out without the individual being aware of it; this is quiet breathing or *eupnea.* Inspiration is then accomplished by contraction of the diaphragm and of the external intercostals, but no other muscles participate actively; as a matter of fact, there are some associated movements, such as expansion of the nostrils and abduction of the vocal cords, and the expiratory muscles probably are inhibited automatically when the inspiratory muscles contract, but the inspiratory effort of eupnea is distinguished from that of forced or labored breathing (*dyspnea*) by the ease and comfort with which it is performed. The expiratory phase of eupnea involves no active muscular contraction; there probably are changes in tone of the expiratory muscles—a decrease during inspiration and an increase during expiration—but there are none of the active expiratory movements that characterize dyspnea.

When it becomes necessary for the individual to move more air in and out of his lungs the contractions of the diaphragm and external intercostals increase in strength and the muscles which run from the ribs and sternum upward—the accessory muscles of inspiration—come into play. The expiratory muscles also begin to contract actively so as to hasten the emptying of the lungs and to make it more complete. If this does not occur an increase in depth of breathing will necessarily slow the rate: it is only by a commensurate increase in the activity of the expiratory muscles that both rate and depth of breathing can be increased simultaneously (Fig. 214). But when breathing has been increased enough to bring the expiratory muscles into action the accessory muscles of inspiration are also active and the subject knows that he is breathing heavily; he can no longer remain unaware of respiration as he does when breathing quietly. The term *dyspnea* implies labored breathing, and it also implies that the accessory inspiratory and the expiratory muscles participate in the act.

The Relative Parts Played by Costal and Diaphragm Movements in Pulmonary Ventilation

According to Keith[98] the area of the diaphragm in contact with the lungs is about 250 sq. cm. If the diaphragm descends 10 mm. there would be an increase of 250 ml. in the volume of the thorax and therefore in the volume of air in the lungs. This is about half the amount of an ordinary tidal inspiration, and the costal and diaphragm mechanisms thus appear to participate about equally during quiet breathing. There is little doubt, however, that the costal mechanism alone can meet not only the resting requirements for pulmonary ventilation but also the increased requirements associated with violent activity. For example, Pancoast, Baetjer and Dunham[122] examined a famous middle-distance runner and found his diaphragmatic movements greatly restricted by adhesions, in the presence of which he had established two world's records. On the other hand, when the costal respiratory mechanism is paralyzed by spinal anesthesia extending to the upper thoracic region and respiration becomes purely diaphragmatic, both respiration and circulation become greatly impaired.

Quiet breathing in men is largely diaphragmatic, in women largely costal. Much of the difference is doubtless due to restriction of abdominal movements by the tighter clothing worn by women, but the habit of costal respiration is decidedly advantageous during preg-

*For the causes of forced breathing, see pages 648 and 675.

nancy. In either sex an increase in pulmonary ventilation above the resting level is accomplished mainly by increased costal movements, but increased activity of the diaphragm must also occur if the movements are to be effective. Otherwise the abdominal contents will be drawn upward by the increased negative pressure resulting from the enlarged costal cage and also pushed upward by the increased expiratory activity of the abdominal muscles which accompanies an increase in pulmonary ventilation. Unless this encroachment on the thoracic cavity is antagonized by increased diaphragmatic activity, the capacity of the cavity to hold air may actually be decreased although the chest is greatly expanded. Keith[92] points out that the thorax can be expanded so that abdominal viscera are drawn into the thoracic cavity instead of air, by contracting the abdominal muscles and failing to contract the anterior part of the diaphragm while a maximal costal inspiration is made. In this way the chest can be tremendously enlarged, but there is no necessary relationship between the extent of the expansion and the amount of air taken into the lungs. It is only by coordinated activity of the costal, diaphragmatic, and abdominal muscles that increased respiratory efforts can effectively increase pulmonary ventilation.

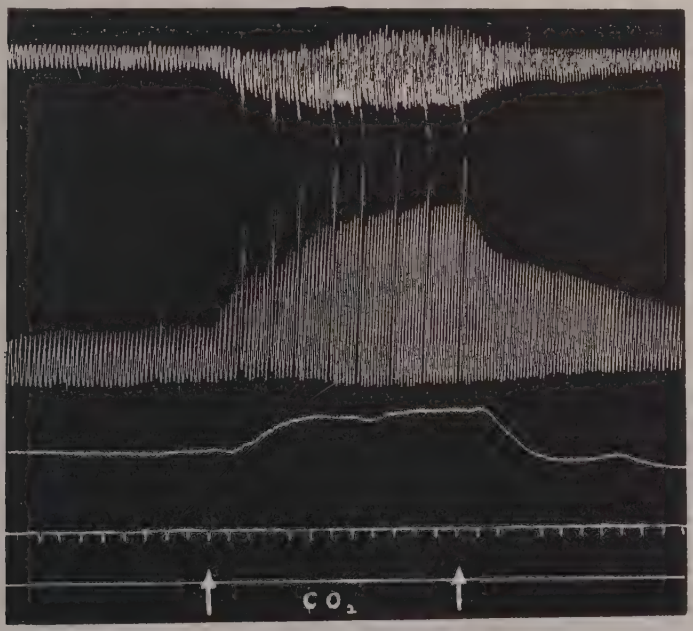


Fig. 214.—Dyspnea in a cat under ether anesthesia. Upper record: intrathoracic pressure—downstroke = inspiration. Middle record: volume of respiration (body plethysmograph) —upstroke = inspiration. Arterial pressure, time in five-second intervals, and signal tracing are also shown. Between the arrows air containing 8.5 per cent CO_2 was inhaled for one minute. Before the inhalation the respiratory rate was 60 per minute, the average depth 31 ml., and the volume of the air breathed in ten seconds was 370 ml. During the first twenty seconds the rate was unchanged but the average depth increased to 61 ml.; expiration was not increased in proportion, as shown by the fall in the upper (expiratory) level of the record of intrathoracic pressure; the volume breathed in ten seconds was 522 ml.; these values represent the effects of increased activity of the muscles of quiet inspiration alone. Then the accessory inspiratory and the expiratory muscles began to participate; after forty seconds of the inhalation, the rate of breathing increased to 84 per minute, average depth to 95 ml., and volume per ten seconds to 1048 ml.; the increased vigor of the inspiratory movements is shown by the greater downward excursion of the lever recording intrathoracic pressure, while the increased force of expiration is shown by the higher level and the sharper upstroke of the same lever during expiration. By the end of the inhalation the rate was 90 per minute, the average depth 97 ml., and the volume per ten seconds 1064 ml. (From Schmidt and Harer: J. Exp. Med. 37: 47, 1923.)

THE PRESSURE CHANGES

The Intrapulmonary Pressure

The pressure of the air in the respiratory passages is readily measured by inserting into one nostril a tube connected with a manometer. At each normal inspiration the manometer registers a negative (subatmospheric) pressure of 2 or 3 mm. Hg and at each quiet expiration a positive pressure of about the same degree. The same changes presumably take place throughout the air-bearing passages and spaces. If there is an interference with the free passage of air in and out of the lungs the changes in intrapulmonic pressure may become much greater than this. The greatest possible expiratory pressure is created by attempting to blow with the mouth and nostrils closed; it can be measured by blowing into a manometer and may amount to more than 100 mm. Hg. Similarly, the greatest possible negative pressure on inspiration, measured by attempting to inspire through a tube connected to a manometer, may equal –70 mm. Hg. Such pressures are seldom attained except experimentally, but intrapulmonic pressures approaching them may be found when the free passage of air is impeded, as it may be voluntarily during defecation or parturition, or in pathological conditions, such as spasm of the glottis, diphtheria, bronchial asthma, or the presence of a foreign body.

The Intrapleural Pressure

If an opening is made in the thoracic walls of a living animal or of one recently dead, air enters and the lungs collapse. This indicates that even when the respiratory muscles are relaxed (i.e., in passive expiration) there must normally be a subatmospheric pressure between the thoracic wall and the outer surface of the lungs. If the puncture is made by a needle which is connected to a manometer, this pressure at passive expiration is found to be about –5 mm. Hg. During quiet inspiration it becomes about –10 mm. Hg. If the respiratory passages are obstructed the pressure may become –70 or –80 mm. Hg during forced inspiration, +100 mm. Hg during forced expiration.

It is the alternating changes in intrapleural pressure that are responsible for the changes in intrapulmonary pressure and these in turn cause the movement of air in and out of the lungs with each respiration. In the normal living animal the lungs completely fill every part of the thorax that is not occupied by other structures (heart, blood vessels, esophagus, trachea, bronchi, lymphatics, etc.). There is normally no space between the parietal and visceral layers of the pleura, and any change in volume of the thoracic cavity means an equal change in the volume of air in the lungs. This is because the pressure existing on the outer surface of the lungs is normally subatmospheric.

Changes in intrapleural pressure also have important effects upon the circulation; these are discussed on page 497.

The Cause of the Negative Intrapleural Pressure.—In the fetus in utero the lungs contain no air, but even though they are completely collapsed they fill the thorax as completely as in the adult because the thorax has never been expanded. When the first breath of air is drawn, the thoracic cage is expanded and remains so throughout life; the increased space so created is filled by air which enters the lungs at the first breath, and from that time on the lungs are never again completely empty of air. This fact is utilized in legal medicine to de-

termine whether a child died before or after birth; if the former the lungs sink in water, if the latter they float.

The permanent expansion of the lungs as the result of the first breath means that the pulmonary tissues are stretched and the elastic elements therefore tend constantly to recoil. The lungs contain a considerable amount of smooth muscle and elastic tissue, and recent work indicates that the changes in volume of the lungs which occur during inspiration and expiration are associated with considerable elongation and shortening of smooth muscle and elastic fibers. Since even a maximal expiratory effort leaves the lungs far more stretched than they were in the fetal state it is obvious that the smooth muscle and elastic tissue of the lungs must be continuously on the stretch and therefore continuously attempting to pull the lungs away from the chest wall. This is the force that is responsible for the negative pressure in the pleural cavity.

THE VOLUME CHANGES

When the inspiratory muscles contract the volume of the thoracic cavity enlarges, intrapleural pressure falls further below the atmospheric level, and air rushes into the lungs through the respiratory passages in volume equal to the increased size of the cavity. The process is reversed when expiration occurs. The volume of air which enters and leaves the lungs with each quiet respiration is known as the *tidal air;* it amounts to about 500 ml. in normal adults. The volume of air that can be taken in over and above an ordinary tidal inspiration is called the *complemental air;* it is normally about 1500 ml. The volume that can be expelled after a quiet (tidal) expiration is the *supplemental air;* this also is about 1500 ml. Adding these three, we have the *vital capacity*—the volume of air that can be expelled by the most vigorous expiratory effort after the deepest possible inspiration; it is normally about 3500 ml. The volume of air remaining in the lungs after the supplemental air has been expelled is known as the *residual air;* it amounts to about 1500 ml. and it represents the volume of air that can be recovered from the lungs when they are made to collapse by admitting air to the pleural cavities. Even then there will remain in the lungs some air that cannot be removed because the thin-walled terminal air passages collapse before all the air can be expressed; this part of the residual air is sometimes called the *minimal air.* The volume of residual air can be measured in a dead animal by clamping the trachea before opening the thorax and permitting the air subsequently to escape through the trachea into a spirometer, or to displace water in an inverted graduated cylinder.

The Residual Air and Midcapacity of the Lungs.—During muscular exercise the residual air of the lungs is increased and the vital capacity decreased. This causes the lungs to assume a more inflated condition between breaths, a greater midcapacity. These changes may serve as a physiological method for increasing the efficiency of aeration of the blood, partly because the pulmonary vessels become dilated and the blood flow through the lungs is favored, and partly because of the more thorough ventilation of the alveoli and the greater volume of the reserve and supplemental airs left in the lungs at the end of expiration. This prevents violent changes in the tension of CO_2 and O_2 in the blood.

Patients suffering from dyspnea, particularly those suffering from cardiac dyspnea, cannot breathe as comfortably when lying as when sitting. This condition is known as *orthopnea.*

The Vital Capacity.—Peabody and Wentworth[124] have called attention to the fact that the tendency of patients with heart disease to become dyspneic more readily than do healthy subjects depends largely on their inability to increase the depth of the respiration in a normal manner. This inability to breathe deeply corresponds to a diminished vital capacity of the lungs.

In normal adults the averages shown in Table XVII were secured from a large series of clinical cases. The subjects are grouped into two classes, each group being subdivided according to height.

It would appear that in normal persons the vital capacity is at least 85 per cent, and almost always 90 per cent or more, of the standard adopted for each group. In elderly persons a slight decrease from these standards may be expected.

TABLE XVII

THE VITAL CAPACITY OF THE LUNGS OF NORMAL MALES

GROUP	NUMBER STUDIED	HEIGHT IN FEET AND INCHES	NORMAL VITAL CAPACITY ML.	NUMBER WITHIN 10% OF NORMAL	HIGHEST VITAL CAPACITY	LOWEST CAPACITY VITAL	HIGHEST %	LOWEST %	NUMBER BELOW 90% OF NORMAL
I	14	6′ +	5,100	9	7,180	5,030	141	99	0
II	44	Over 5′ 8½″ to 6′	4,800	41	5,800	4,300	121	90	0
III	38	5′ 3″ to 5′ 8½″	4,000	31	5,080	3,450	127	86	1
		THE VITAL CAPACITY OF THE LUNGS OF NORMAL FEMALES							
I	10	Over 5′6″	3,275	5	4,075	2,800	124	86	2
II	13	Over 5′4″ to 5′6″	3,050	9	3,425	2,660	112	88	2
III	21	5′4″ or less	2,825	16	3,820	2,500	135	89	1

(Peabody and Wentworth)

Table XVIII shows that there is a remarkably close relationship between the clinical condition of cardiac patients, particularly as regards the tendency to dyspnea, and the vital capacity. Determination of the vital capacity, therefore, affords a clinical test as to the functional condition of the heart, and

TABLE XVIII

THE RELATION OF THE VITAL CAPACITY OF THE LUNGS TO THE CLINICAL CONDITION IN PATIENTS WITH HEART DISEASE*

GROUP	VITAL CAPACITY %	NUMBER OF CASES	MORTALITY %	SYMPTOMS OF DECOMPENSATION %	WORKING %	REMARKS
I	90 –	25	0	0	92	Few symptoms referable to heart.
II	70 to 90	41	5	2	54	History of dyspnea with exertion, yet able to do moderate work.
III	40 to 70	67	17	89	7	Dyspnea with moderate exercise. Few able to work.
IV	Under 40	23	61	100	0	Bedridden, with marked signs of cardiac insufficiency.

(Peabody and Wentworth)

*Certain patients were tested several times and, owing to changes in the vital capacity they appear in more than one group. In the "mortality" column they are included only in the lowest group into which they fall. "Symptoms of decompensation" indicate dyspnea while at rest in bed or on very slight exertion. Under "working" are included only those actually at work, and able to continue. Many other patients in Group II were able to work, but they are not included as they were still in the hospital.

compensated patients who do not complain of dyspnea on exertion have a normal vital capacity. As a patient improves, his vital capacity tends to rise; as he becomes worse, it tends to fall. In other diseases in which mechanical conditions interfere with the movements of the lungs, the tendency to dyspnea also corresponds closely to the decrease in the vital capacity. The cause of the decrease in the vital capacity in cardiac decompensation is difficult to explain satisfactorily. It may be the limitation in the movements of the lungs produced by engorgement of the pulmonary vessels (see page 650).

It has become more and more evident, since Peabody and Wentworth's researches, that a determination of the vital capacity is of great importance in the diagnosis and prognosis of several diseases, including heart disease and tuberculosis. It is particularly important in gauging the effects of treatment. In order that the value actually found in a given patient may be compared with the value for a healthy individual of the same body build, Lundsgaard and van Slyke[105] and Dreyer[49] have worked out several ratios, the most useful of which is one based on the body surface. The body surface is determined from measurement of height and weight by the graphic chart of DuBois, the use of which is explained on page 745.

The vital capacity can be satisfactorily measured by using a simple spirometer of about 8 liters capacity; three trials should be allowed, the largest expiration being recorded. The average value for vital capacity in liters divided by the body surface in square meters is 2.61 liters and for women 2.07 liters per sq. m. (e.g., vital capacity = 5,300 l.; body surface 2.01, therefore, ratio = 2.63). The deviation from the values should not be beyond 15 per cent, the great proportion of normal persons being within 10 per cent of the above averages. Athletes give decidedly higher values and old people give lower ones.

Pneumothorax

It used to be considered that free entrance of air into one pleural cavity caused the lung on that side to collapse, without much change occurring in that of the opposite side, but Graham,[65] Lenhart, and others have shown that such is not the case. In the first place the older view that the mediastinal structures in man form a more or less rigid partition between the two pleural cavities can easily be shown to be erroneous, by x-ray examination of the thorax. Thus, Graham found, in the case of a man immediately after death from peritonitis, that the admission of even a small quantity of air (pressure 0.65 mm. Hg) into one pleural cavity resulted in marked deflection of the trachea and heart to the opposite side, and this became very pronounced when the air pressure was raised. In consequence of this mobility of the mediastinum, the pressures in the pleural spaces in man run almost parallel with each other even when there is an alteration in pressure in one pleural cavity. Similar results were obtained on dogs, and they indicate that the thorax may be considered as one cavity. In unilateral pneumothorax, therefore, both lungs are affected almost equally when the opening is small.

As to whether an animal will survive a pneumothorax depends on (1) the amount of air which enters by the wound with each inspiration and (2) the ability to compensate for the resulting encroachment of the respiratory surface (Graham). An estimate of what degree of pneumothorax can be tolerated is obtained by measurement of the vital capacity; the greater this is the larger may be the opening. If the capacity is small asphyxia is inevitable, however great may be the inspiratory effort. There is less danger from pneumothorax when pleural adhesions prevent the lungs from collapsing. It is probable that failure of some investigators to observe equality in pressure changes in the

two pleural cavities has been due to obstruction of the open end of the trochar in the thorax by the lung coming against it. To avoid this, a small cushion of air should be injected near the cannula. On account of the opening in the chest wall, not only is the reserve air of the lungs diminished, but the total volume of each breath tends to be reduced, so that a condition of anoxemia supervenes. When this threatens, oxygen should at once be administered. To compensate for the reduction in tidal air the inspiratory movements are increased, and, provided there be no obstruction in the air passages, this increase is usually sufficient to prevent fatal anoxemia, even with a fair-sized opening. Naturally this does not apply when there is pneumonia, or pulmonary edema, or uncompensated heart disease. If the patient cannot respire deeply enough to make his vital capacity equal to his tidal air he may succumb, even when the thoracic wound is a small one. After closure of the wound breathing improves immediately, because there is now no competition between the air entering through the wound and that entering by the trachea. The closure should be made at the end of an expiration so as to leave as little air in the pleural space as possible and thus facilitate the creation of the normal negative pressure. Indeed, if this space be filled with air under positive pressure before the wound is closed, there is risk of asphyxia, especially in cases in which the vital capacity is low. This fact must be borne in mind in bringing about collapse of the lungs for therapeutic purposes, as in tuberculosis.

It is evident from the above that it is unsafe to establish open drainage of the thorax for empyema in the pneumonic stage of the disease. In this condition the vital capacity is so low that it is impossible for the patient to increase the respirations sufficiently to obtain the necessary tidal air. Another advantage of waiting until after the pneumonia has subsided is that the pus becomes circumscribed by adhesions. Since the adoption of these principles the mortality from acute empyema has dropped from about 60 to 10 per cent.

Other effects of pneumothorax are the circulatory disturbances, due to interference with the venous blood flow in the thorax, and a remarkable chilling effect, so that the body temperature falls rapidly.

When a large opening must be made surgically in the thorax, artificial respiration with oxygen-rich air, through a face mask, should be instituted and maintained until the wound is closed or diminished to a very small opening. The air remaining in the pleural space soon becomes absorbed (usually within a week or two). There is no justification for the belief that nitrogen remains unabsorbed longer than air. Soon after the thoracic wound is closed, the entrapped air assumes the same composition as alveolar air.

Alveolar and Dead Space Air

Each moiety of respired air so far considered is simply a volume of air that can be recovered from the lungs under certain conditions without any reference to the part of the respiratory system from which it came or to the rôle played by it in the gaseous exchange in the lungs. From the physiological standpoint the all-important volume of air is that which comes into contact with the epithelium through which gases are exchanged between the blood and the air; this is known as *alveolar air*. The volume of air which fills the respiratory passages, through the walls of which there is no gas exchange with the blood, is the *dead space air*. To understand the significance of these terms it is necessary to review briefly some of the salient features in the structure of the lung.

The general arrangement of the air-bearing structures is similar to a tree whose trunk (the trachea) divides into two main branches (the bronchi) which give rise in turn to two smaller branches on the left and three on the right, one going to each lobe of the lung. These divide dichotomously (Macklin[109]) into successively smaller branches until finally the *terminal bronchioles* are reached. Each of these continues into one, two, or more respiratory bronchioles, and each of these breaks up in turn and radiates conelike into 2 to 11 *alveolar ducts;* from these the *alveolar sacs* and *alveoli* finally arise. The tracheobronchial system up to and including the bronchioles is only a conducting pathway for the air; the *respiratory bronchioles* have a few alveoli and are therefore partly respiratory though mainly conducting; the alveolar ducts have numerous alveolar sacs and alveoli as outpouchings and are both conducting and respiratory, while the alveoli are purely respiratory; alveolar sacs are simply groups of two to four or more alveoli. The term *atrium* was formerly given to the space between the alveolar duct and the alveolar sacs, especially at the end of the duct, but recent evidence indicates that this is probably part of the alveolar duct and not a separate entity (Willson,[163] Macklin,[109] Maximow[112]). The arrangement of the finer air passages and surfaces is shown in Fig. 215.

The air-conducting tubes have rigid walls, due to the presence of cartilage in the form of rings in the trachea and primary bronchi, of overlapping plates in the intrapulmonary bronchi. In bronchioles with a diameter of 1 mm. or less, cartilage is lacking and these

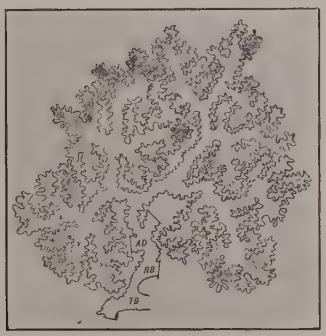


Fig. 215.—Arrangement of terminal air passages and alveoli in human lung. All the air sacs and alveoli (shown in gray) arising from one branch of an alveolar duct (*AD*) which has arisen from one of the two respiratory bronchioles (*RB*) resulting from the division of a terminal bronchiole (*TB*) are shown projected in one plane. The areas marked *X* correspond with the atrium of Miller. From a reconstruction of the human lung by Willson.[163] (From Maximow and Bloom: Textbook of Histology, Philadelphia, 1934, W. B. Saunders Co.)

finer passages are therefore easily collapsed. Smooth muscle is found in the walls of all of the air passages, including the alveolar ducts; it is relatively most abundant in the terminal bronchioles, where complete obliteration of the lumen can be produced by contraction of the muscle (Macklin[109]); peripheral to this point the muscle becomes more delicate and the prevalent belief is that the walls of the alveoli contain no muscle at all (Macklin, Maximow[112]). The epithelium of the rigid tubes is columnar and bears cilia which beat toward the mouth; the surface is bathed with mucus secreted by glands in the subepithelial layers. No gas exchange can occur down to this point. In the respiratory bronchioles, which begin with a diameter of about 0.5 mm., the columnar epithelium of the air passages undergoes transition to a flattened cuboidal type, but whether this covers the entire alveolar surface in adult mammals is at present uncertain; it is possible[110] that the epithelial covering is lacking over large areas, the capillary endothelium lying directly exposed to the air in the alveoli. Even if the epithelial coat is intact throughout, the alveolar walls consist only of this and a tenuous supporting framework. This is where the pulmonary gas exchange occurs (see Chap. XLII).

The term *alveolar air* really means simply expired air which is in gaseous equilibrium with the arterial blood leaving the lungs. As we shall see later

(Chap. XLII) it is unlikely that air can actually be expelled from the alveoli without collapsing the lung, but the air in the alveolar ducts can be expelled by a vigorous expiration and experience has shown that this air is practically in gaseous equilibrium with the arterial blood when the subject is at rest.

To collect alveolar air the method of Haldane and Priestley[68] has been found most satisfactory.* The subject breathes quietly through a tube and then makes a maximal forced expiration, at the end of which a sample of air is collected for analysis. One such collection is made after a normal expiration, another after a normal inspiration. The O_2 and CO_2 contents of two samples are determined separately and the average of the results is taken to represent the O_2 and CO_2 contents of the alveolar air.

The average CO_2 content of the alveolar air is 5.6 per cent, representing a tension of 40 mm. Hg; the average O_2 content is about 14 per cent, representing a tension of 100 mm. Hg.†

It has been found by experience that an expiration of 400 ml. suffices to displace the air in the dead space and to expel air that is constant in its composition under constant conditions. This is alveolar air, and the expiration required to collect it must be more than 400 ml. When the subject is at rest the CO_2 tension of alveolar air collected in this way is equal to that of the arterial blood; the oxygen tension is normally higher in the alveolar air than in the blood by 5 to 25 mm. (see Chap. XLVII) and complete equilibrium with respect to oxygen is not to be expected. During exercise the average CO_2 tension calculated from the two Haldane-Priestley samples is higher than that of the blood; the sample expelled after the inspiration is closer to CO_2 equilibrium with the blood. If we define alveolar air as air which has the same CO_2 tension as arterial blood, we must conclude that the technique for collecting it cannot be the same under all conditions, but the method of Haldane and Priestley usually indicates at least the order of magnitude of the arterial CO_2 and its deviation from the normal (Peters and van Slyke[126]).

Dead space air cannot be measured directly, but its volume can be estimated by determining the extent to which alveolar air is diluted in leaving the lungs, as evidenced by the difference in CO_2 content between total expired air and alveolar air. Dead space air is assumed to have the same composition as inspired air. The necessary data are (1) the volume of the tidal respiration, (2) the percentage of CO_2 in the alveolar air, and (3) the percentage of CO_2 in the tidal expired air. Suppose these to be 500 ml., 6 per cent, and 4 per cent respectively; then the volume of alveolar air must be $500 \times \frac{4}{6} = 333$ ml., and the dead space 167 ml. The dead space of an adult at rest is estimated as 125 to 200 ml., with 150 ml. as a fair average.

*Mackay (J. Physiol. 98: 73, 1940) has recently cast doubt upon the possibility of collecting alveolar air by this method.

†Room air at sea level, when freed of water vapor, contains 20.93 per cent O_2 (by volume), 0.03 per cent CO_2, and a residue, designated as nitrogen, of 79.04 per cent; this residue contains small amounts of other gases (argon, helium, hydrogen), but since all of these are "indifferent gases" like nitrogen (i.e. they only dilute the oxygen and do not enter into the gas exchange) it is perfectly proper to regard this, the largest fraction of the inspired air, as consisting entirely of nitrogen.

The tension (= partial pressure) of a gas is the fraction of the total atmospheric pressure which it exerts. At sea level the total pressure is 760 mm. Hg. But in calculating the tension of a gas in the expired air allowance must be made for the fact that it is saturated with water vapor, which, at 37° C., exerts a tension of 47 mm. Hg. The total pressure of the dry combined gases (O_2, N_2, CO_2) in the expired air is therefore 760-47 = 713 mm. If we take the figures given above for the percentages of O_2 and CO_2 in the alveolar air (i.e. O_2, 14 per cent; CO_2 5.6 per cent) the corresponding tensions would be:

$$\text{Oxygen } \frac{14}{100} \times 713 = 100 \text{ mm.} \qquad \text{Carbon dioxide } \frac{5.6}{100} \times 713 = 40 \text{ mm.}$$

It is certain, however, that a figure such as this represents the average size of a space that changes greatly in capacity during respiration, not a space that has a fixed size. As we shall see later (page 617), the capacity of the respiratory passages increases with inspiration and decreases with expiration, and it is probable that a large part of the tidal air is accommodated by changes in size of the so-called dead space; the alveoli are ventilated by diffusion of air from the air passages into them and seem to change little if at all in size during the respiratory cycle. The significance of the terms *alveolar air* and *dead space air* is now quite different from what it was when the alveoli were supposed to enlarge and shrink with respiration and the air passages were regarded as constant in size. On the whole, it would be better to drop the term *dead space* entirely and to call the alveolar air effective air, as Peters and van Slyke[126] suggest. This has the advantage that it avoids commitment as to the source of the air in question while suggesting at the same time the physiological rôle which this air plays in respiration.

The Effects of the Respiratory Movements on the Lungs

The changes produced in the dimensions of the lungs by the inspiratory expansion of the thoracic cavity are not uniform, since different parts of these structures are not equally extensible. From an anatomical standpoint, the lungs may be divided into three zones: (1) The inner or root zone containing the bronchus, artery, and vein, and their main subdivisions. The large amount of fibrous tissue in this region offers great resistance to any expanding force. (2) The intermediate zone, containing the vascular and bronchial ramifications radiating toward the surface of the lungs, with pulmonary tissue implanted between the rays. This part of the lungs has varying degrees of extensibility, the pulmonary tissue having the most and the vascular and bronchial the least. (3) The outer zone, perhaps 25 to 30 mm. in depth, composed of pulmonary tissue and equally extensible throughout (Keith). The expansion of the lung is accomplished by a moving apart of the less extensible rays of tissue so as to permit the expansion of the more extensible pulmonary tissue between them. Keith compares the mechanism to that seen in the opening of a Japanese fan.

Because the lung expands in the direction of least resistance, study of the inflated dead lung does not reveal the normal expansion brought about by the thoracic movements. In the living body expansion is more limited in some regions than in others. Of the five areas which may be distinguished on the surface of the lungs, three are in contact with relatively immovable regions of the thoracic cavity, and therefore cannot be expanded directly. These are: the *mediastinal surface,* in contact with the pericardium and the structures of the mediastinum; the *dorsal surface,* in contact with the spinal column and the posterior aspect of the thoracic cage, and the *apical surface.* The motions of the first pair of ribs and the manubrium expand chiefly the anterior and ventrolateral part of the apex of the lung, and have only an indirect influence on the dorsal part of the apex; i.e., the part lying directly in front of the necks of the first and second ribs, the most common site of pulmonary tuberculosis. Indeed, the dorsal part of the apex moves downward, instead of upward, on inspiration. It moves down with the diaphragm.

The two surfaces of the lungs which are directly expanded are the diaphragmatic and the ventrolateral or sternocostal. Meltzer[115] found that the negative

pressure in the thorax during inspiration was least along the relatively stationary walls of the thorax, and greatest in the regions nearest the diaphragm. From this he concludes that some of the expanding force is lost as it passes through the lungs to the surfaces of indirect expansion. Many observers have claimed that the expansion of the lung does not take place instantaneously and equally throughout the organ. This supposition is supported by the fact that the region immediately surrounding a localized consolidation has increased resonance, which would not be the case if the relaxation produced were equally distributed throughout the lung.

The root of the lung, which has generally been regarded as more or less fixed, undergoes in normal breathing a definite forward, downward, and outward movement, in which the heart shares (Keith). The movements of the lower ribs and diaphragm are responsible for the expansion of the lower lobes and dorsal portion of the upper lobes of the lungs, whereas the movement of the upper five ribs expands the anterior portion of the upper lobes. The relative infrequency of pleuritic friction-sounds and pain over the upper lobes, as compared with their frequency over the lower lobes, is explained by the fact that the expansion of the upper lobes is accomplished with little displacement of the pleural surfaces, whereas in the lower lobes expansion is accompanied by a gliding of the lungs across the ribs. It is on this account that after its removal postmortem no rib markings are visible on the upper anterior regions of the lung inflated with air. It is important to remember that all portions of the lungs do not open up equally on inspiration. When the tidal air is normal in volume, this is of little consequence, but when it is reduced, as in shallow breathing, the only alveoli which will be adequately ventilated will be those of the more expansile regions. The result of the shallow breathing will of course be that the blood leaving the well-ventilated portions will be saturated with O_2 and have a relatively low CO_2 tension, whereas that from ill-ventilated portions will be unsaturated with O_2 and overloaded with CO_2. In the mixed pulmonary blood which enters the left auricle under these conditions the tension of the gases will therefore not be in equilibrium with the alveolar air of any one portion of the lungs. Recognition of this source of fallacy is particularly important when attempts are made to correlate the gases of the blood and alveolar air, especially in diseased conditions.

CHAPTER XXXIX

THE RESPIRATORY CENTER: ITS LOCATION, ORGANIZATION, AND ACTIVATION

At inspiration during quiet breathing the diaphragm and the external intercostals contract in unison, the alae nasi dilate, and the vocal cords are abducted; the expiratory muscles probably relax at the same time and, as we shall see later (page 617), the smooth muscle of the air passages seems to relax also. During eupnea inspiration is smooth, easy, and effortless, and expiration occurs by virtue of the recoil of the elastic tissues of the lungs and thorax, the atmospheric pressure exerted on the chest wall, and probably the return of tone to the expiratory muscles. When it is necessary to increase the volume of air breathed, as in dyspnea, the accessory muscles of inspiration become active during the inspiratory phase and the expiratory muscles contract during the expiratory phase. All this can occur in an unconscious individual (e.g., in one under the influence of an anesthetic drug) or in a decerebrate animal. Obviously there must be some highly developed coordinating system to account for the contraction of the various muscles at the proper time and with the proper strength.

The respiratory muscles belong (with the exception of those of the bronchial passages) to the system of voluntary or striated muscles. They can contract only when they receive impulses over their motor nerves, and the nerves pass out to them from the brain stem and spinal cord. The mechanism which activates and coordinates the respiratory muscles must therefore lie in the central nervous system. It must be able to initiate impulses to the inspiratory and expiratory muscle groups alternately. It must coordinate the activity of the various muscle groups so that the accessory inspiratory muscles come into play when needed and the expiratory muscles likewise. It must respond to various afferent nerve impulses, especially to impulses from the lungs themselves. It must also be governed by chemical factors, for the main task of respiration is to maintain the oxygen supply of the tissues and the amount of air breathed must correspond with the amount of oxygen needed by the body. And all this must be done without necessarily involving the higher parts of the brain, although to account for the fact that one can modify one's respiration voluntarily it is necessary that the regulating mechanism be susceptible to voluntary control. The part of the central nervous system in which the impulses to the respiratory muscles originate and are coordinated is called the *respiratory center*. Although it is not a center in the sense of being a sharply demarcated group of nerve cells (see next page) the term is so convenient and has come into such universal use that it will be used in this book to designate the functionally integrated group of nerve cells and fibers in which the impulses to the respiratory muscles have their origin and coordination.

If we compare the general scheme of the regulation of respiration with that of the regulation of the circulation, we shall find several interesting points of similarity. In the circulation the flow of blood is regulated by the interplay of the contraction of cardiac muscle and the tone of the smooth muscle of the blood vessels; in the respiration the flow of air in and out of the lungs is regulated by the interplay of the contraction of the re-

spiratory muscles and the tone of the smooth muscle of the air passages. In both the muscular contractions which furnish the motive power exhibit a regular rhythm. In both the rhythm arises in a part of the system whose specialized function it is to set the rhythm for the entire system: the sinus node in the heart is comparable with the respiratory center in this respect. In both cases the rhythm is due to the fact that the tissue in which it originates becomes less excitable as a result of its activity and cannot repeat the discharge until it has recovered. Thus a constant chemical stimulus gives rise to a rhythmically repeated activity, in both the sinus node and the respiratory center. In both cases the impulse which leads to contraction is conducted from the point of origin in such a way that the resulting muscular contractions are properly coordinated and take place in proper sequence. In the heart the impulse arises and is conducted in that organ itself, but in the respiratory system the origin and conduction take place entirely in nervous tissue. In both cases the intrinsic rhythm is tonically modified by nerve impulses acting on the structure in which the rhythm originates, and in both there are two sets of such impulses—one inhibitory, the other excitatory to the intrinsic rhythm. In both, the afferent nerve impulses having the greatest effect upon the rhythm originate in specialized stretch receptors located in a peripheral part of the system—those in the aortic arch and carotid sinuses in the case of the heart, those in the extreme periphery of the air passages in the case of the respiration. The effects of reflex excitation of the vagus on the cardiac rhythm are approximately comparable with those of the impulses set up by inflation of the lungs upon the respiratory rhythm, i.e., both are inhibitory to the respective rhythms; the effects of accelerator impulses upon the heart are analogous to the respiratory effects induced by collapse of the lungs in that both accelerate the respective rhythms. The stimulus which activates the stretch receptors is furnished in both cases by the muscular efforts which it is their task to moderate—cardiac systole and intravascular pressure in the one, enlargement of the thorax and distention of the lungs in the other. As far as the general plan is concerned, the main difference is that whereas the heart is a self-contained rhythmic mechanism that requires only quantitative regulation, the respiratory muscles (which are the propelling force of the respiratory system) are dependent upon the central nervous system not only for coordination and sequence of contractions but even for the impulse to contract at all.

THE LOCATION OF THE RESPIRATORY CENTER

If the cerebrospinal axis of an animal is destroyed piece by piece from above downward, breathing is not characteristically affected until the anterior border of the pons is reached. After removal of all cerebral tissue above the pons, an animal often breathes more slowly for a time but respiration is unaltered in character and it responds to nervous and chemical influences in a normal manner and approximately to a normal extent. Thus, although there is no doubt that respiration can be affected by impulses from the higher parts of the neuraxis (as evidenced by the respiratory effects of emotional disturbances or of strong stimulation of the special sense organs) it is clear that such factors are only incidental and that the automatic control does not require the participation of any part of the system anterior to the pons. When sections are made across the pons, however, alterations in breathing begin to be encountered, and these become progressively more frequent and more marked as the level of the section moves downward. Finally, transection of the medulla, at or below the level of the tip of the calamus scriptorius, causes immediate and usually permanent cessation of breathing. Hence the essential parts of the respiratory center lie in the pons and upper two-thirds of the medulla, and more in the latter than in the former.

Attempts at further localization of the center yielded inconclusive results until recently, although the burden of evidence strongly suggested that the nerve cells comprising it are not localized in a compact mass but are scattered throughout the reticular gray matter *(formatio reticularis grisea)* of the medulla

and lower pons. Recent physiological studies have proved this beyond reasonable doubt in the dog[61] and cat,[154, 129, 130, 131, 132] and the observations of Finley[55] on two children who died of primary respiratory failure indicate that it is also true in man. In both dog and cat the cells comprising the respiratory center occupy a stretch of the ventral reticular formation of the medulla approximately coextensive longitudinally with the inferior olivary body.

The fact that the automatic control of respiration is accomplished in one part of the gray reticular formation of the central neuraxis is interesting in view of the anatomical peculiarities of this tissue. As shown in Fig. 216, the formatio reticularis is characterized by (1) nerve cells of different sizes scattered in the meshes of (2) nerve fibers which run transversely and longitudinally. In most other parts of the mammalian central nervous system the nerve cells are aggregated into various nuclei and the fibers into definite tracts. Kappers[90] suggests that when this does not occur (as in a reticular formation) it is because the cells are not dominated by any particular set of nerve impulses but serve as the final motor pathway for impulses from a variety of sources, and that the function of such a structure is to coordinate, for a purpose of fundamental importance to the organism, the activity

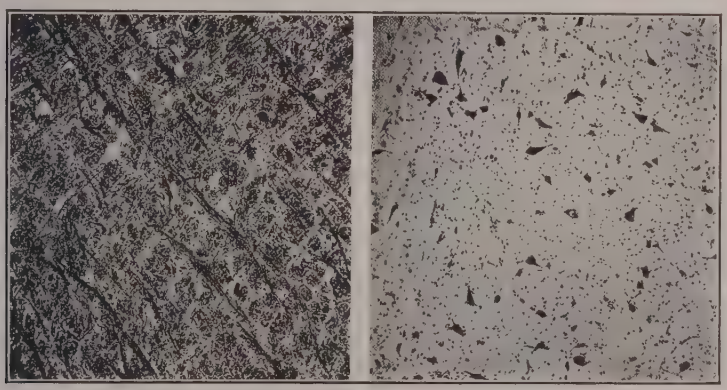


Fig. 216.—Formatio reticularis in the medulla of man. From two adjacent transverse sections, one (on left) prepared with Weigert stain to show fibers, the other (on right) with Nissl stain to show cells. (These sections were kindly furnished by Dr. Helena Riggs.)

of muscles that are innervated through widely separated groups of nerve cells. He points out that there is a reticular formation extending without interruption throughout the medulla and pons, with special developments at three levels, i.e. (from above downward), in the regions of the nuclei of the trigeminal, auditory, and vagus nerves respectively. The last of these—the inferior reticular nucleus—appears from the studies of Pitts[129] to be coextensive if not identical with the inspiratory center in the cat. The functions of the other reticular nuclei remain unknown, but Kappers has suggested that they may be intended to orient the animal's movements with regard to olfactory, visual, tactile, gustatory, and auditory sensations, for purposes of feeding or self-preservation. The inferior reticular nucleus could similarly be regarded as an organization for orienting the animal with regard to afferent impulses carried by the glossopharyngeal and vagus nerves, for these (as we shall see in Chapter XL) are vitally important to the control of breathing; they are the only afferent impulses of which that can be said. Perhaps this organization was originally developed by a water-breathing animal in which among the impulses carried by the vagus and glossopharyngeal nerves were those aroused by changes in chemical composition in the environmental water, and only those animals could survive the transfer to an environment of air in which the reticular cells had developed a new property, viz., that of being directly stimulated by increases in the carbon dioxide tension of their own im-

mediate environment, which is arterial blood. Whether this is true or not (which is, of course, entirely conjectural), the part played by the respiratory center in the adaptation of the organism to its environment depends on its being responsive to precisely the two factors just noted, viz., afferent impulses carried by the glossopharyngeal and vagus nerves, and changes in the carbon dioxide tension of the arterial blood. These ontogenetic considerations are taken up again on p. 597.

The nerve cells in the reticular formation of the pons and medulla presumably are *motor* in function, and the morphology of the structure (Fig. 216) gives strong indication of an organization uniquely adapted for the propagation of a nerve impulse in all directions. An impulse impinging upon any one of these cells from above, or arising in it spontaneously, can be envisaged as spreading throughout the entire system and thus, by inciting other neurons, giving rise to a simultaneous burst of impulses to various motor nuclei at lower levels of the system, such as the anterior horn cells of the spinal cord from which the respiratory muscles are innervated. These inferences from morphological considerations are supported by direct evidence recently obtained by Pitts and his associates[130, 131] who found that relatively weak electrical stimulation through a small electrode inserted into any one of a large number of spots in the region of the inferior reticular nucleus of the cat elicited exactly the same response, viz., a maximal inspiratory effort lasting as long as the stimulus (if maximal); this is the *inspiratory center*. Stimulation in the region just dorsal to this elicited inhibition of inspiration or active expiration; this is the *expiratory* (or *inhibito-inspiratory*) *center* (Fig. 217). In the dog the localization appears not to be as sharp as in the cat but the same types of responses can be obtained.

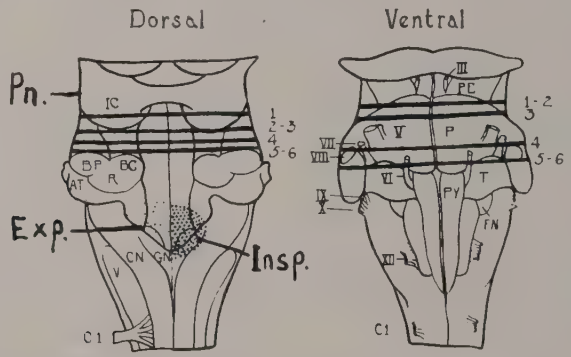


Fig. 217.—Location of the inspiratory, expiratory, and pneumotaxic centers.
Dorsal and ventral views of the brain stem of the cat (cerebellum removed); the upper (cephalic) limit corresponds with the level of an ordinary (intercollicular) decerebration. In the dorsal view the position of the pneumotaxic center (Pn.) is shown in the upper part of the pons, above line 1. (The transverse lines numbered 1 to 6 represent the levels of sections by which this center was found to be inactivated.) The outlines of the inspiratory center (*Insp.*) are indicated by heavy stippling on the right side, those of the expiratory center (*Exp.*) by lighter stippling on the left. Each of the centers is shown only on one side for the sake of clarity, but it must be clearly understood that these centers are symmetrically bilateral.
A, aqueduct; *AT*, acoustic tubercle; *BC*, brachium conjunctivum; *BCX*, decussation of brachium conjunctivum; *BIC*, brachium of inferior colliculus; *BP*, brachium pontis; C_1, first cervical nerve; *CG*, central gray; *CN*, cuneate nucleus; *DT*, descending trigeminal root; *FN*, facial nucleus; *GF*, genu of facial nerve; *GN*, gracile nucleus; *IC*, inferior colliculus; *IP*, interpeduncular nucleus; *LL*, lateral lemniscus; *MET*, mesencephalic trigeminal root; *ML*, medial lemniscus; *MLF*, medial longitudinal fasciculus; *MT*, motor trigeminal nucleus; *NDT*, nucleus of descending trigeminal root; *ON*, oculomotor nucleus; *P*, pons; *PE*, cerebral peduncle; *PY*, pyramid; *R*, restiform body; *RN*, red nucleus; *S*, tractus solitarius; *SC*, superior colliculus; *SN*, substantia nigra; *SO*, superior olive; *ST*, sensory trigeminal nucleus; *T*, trapezoid body; *V*, tuberculum cinereum; *III* to *XII*, corresponding cranial nerves. (From Pitts, Magoun, & Ranson: Am. J. Physiol. 127: 654, 1939.)

THE PHYSIOLOGICAL INTEGRATION OF THE RESPIRATORY CENTER

The respiratory center must be able not only to send out bursts of impulses to the proper muscles at the proper time, but also to adjust the vigor and rate of the respiratory movements to the needs of the body for the uptake

of oxygen and the elimination of carbon dioxide. It is able to do this because of three physiological characteristics, viz., (1) an automatic rhythm subject to modification by nervous and chemical factors; (2) gradations in the sensitivity of different parts of the center with respect to chemical stimuli; (3) a reciprocal innervation between the inspiratory and the expiratory centers. To understand their interrelationships it is necessary first to take up the significance of each of these factors separately.

1. The Automatic Rhythm of the Respiratory Center.—Although there has been general agreement for many years that the respiratory rhythm is normally due in large measure to afferent nerve impulses set up by the respiratory movements, physiologists have long debated whether the center has an intrinsic rhythm of its own when afferent impulses are not acting upon it. This question has considerable theoretical importance because it is reasonable to suppose that the periodic discharge of the respiratory neurons is not peculiar to them but is only a special manifestation of properties that are shared by motor neurons in general. Various types of experimental evidence[167, 4, 5, 82] seemed to indicate clearly that the rhythm is an intrinsic one that is altered but not conferred by afferent impulses. While there is no doubt that the brain stem of a fish[5] or mammal[167, 4, 82] can retain some rhythmic activity—presumably respiratory—although no afferent impulses can reach it from the lungs, chest, or respiratory muscles, this does not prove that the activity is a property of the medullary respiratory center. Lumsden[103] claimed some years ago that the medullary center alone is unable to act rhythmically but can only produce a tonic, sustained contraction of the respiratory muscles, for which he coined the term *apneusis*. He believed that rhythmic activity by this center is due either to periodic inhibition of its activity by impulses carried to it from the lungs via the vagi, or to a rhythm carried to it from another center in the anterior part of the pons, which he designated the *pneumotaxic center* (see Fig. 217). Lumsden's conclusions were called into question by subsequent workers,[75, 157] and until recently it seemed probable that his results depended more on adventitious circumstances such as hemorrhage, trauma, edema, or irritation of nerve fibers, than on the actual presence of cell groups having the functional characteristics postulated by him. Recently, however, Stella[154] and Pitts, Magoun and Ranson[130, 131, 132] have confirmed Lumsden's results and accepted his conclusions in nearly all respects. It should be noted that these workers have used cats exclusively, and while Lumsden claimed to have confirmed his conclusions (with minor discrepancies) in experiments on rabbits, dogs, and monkeys, this has not been done subsequently. The writer believes that the conception derived from these recent studies and now to be presented is probably applicable with minor changes to mammals in general; subsequent investigation in other animals may, however, show that this is not true and that the cat is exceptional in these respects.

According to this conception one or more of the cells of the inspiratory center in the inferior reticular nucleus, impelled by the combination of chemical and nervous influences acting upon it, finally reach a state of such instability of ionic equilibria that a sudden rearrangement (''toppling'') takes place and as a result of this a volley of efferent impulses arises (see page 563). These impulses are conducted throughout the reticular formation by the interlacing fibers characteristic of that structure and all of the cells that are able to respond (i.e., sufficiently unstable) do so simultaneously; the resulting nerve impulses are conducted downward, causing contraction of the corresponding respiratory muscles, and upward, at least as far as the pneumotaxic center in the anterior part of the pons. If no other factor intervenes, the result is sustained contraction of the inspiratory muscles (i.e., apneusis). Pitts has made the interesting suggestion that this is due to rapid recirculation of the excitation wave over one or more pathways in the reticular formation by a process analogous to that involved in auricular fibrillation (page 362); volleys of impulses to the inspiratory muscles would thus be aroused with so brief an interval between them that a tetanus of these muscles results, hence the apneusis. But apneusis does not occur if the vagi are intact, or if the pneumotaxic center is functioning; to produce apneusis, the pons must be transected 2-3 mm. below its anterior border *and* the vagi must be cut or blocked (Stella, Pitts). Impulses from either of these sources can adequately inhibit the process responsible for the apneusis and this appears to be the essence of the intrinsic rhythm of the respiratory center. The inhibitory impulses carried by the vagi are doubtless those aroused by stretching of the lungs during inspiration (page 570); those from the pneumotaxic center pre-

sumably arise from the original inspiratory discharge, part of it being conducted upward to this cell group in which it is transformed into an inhibito-inspiratory (or excito-expiratory) set of impulses which are conducted downward again to the medullary reticular formation.

The outstanding fact of all this is that the discharge of impulses by the medullary center to the inspiratory muscles normally gives rise to a bombardment of this center by a set of inhibitory impulses set up either by the expansion of the lungs (a reflex carried by the vagi) or by the inspiratory discharge itself, acting through the pontile pneumotaxic center. Since the activity of the medullary center is automatically inhibited by way of the pontile center whether any respiratory movement occurs or not, and since (if we accept the conclusions of Lumsden, Stella, and Pitts) the former is incapable of rhythmic activity in the absence of inhibitory impulses either from this source or from the lungs, it follows that the medullary respiratory center is not inherently rhythmic, as it was long believed to be.

2. Gradations in Sensitivity of Different Parts of the Center to Chemical Stimuli.— The fact that in quiet breathing only a few muscle groups (mainly the diaphragm and external intercostals) are actively involved while during dyspnea the accessory inspiratory and the expiratory muscles participate in the act (page 540) probably means that different cells of the reticular formation have different sensitivities to chemical stimuli. Those which innervate the muscles of quiet inspiration evidently have the greatest sensitivity and are perhaps the only ones that discharge impulses under the conditions corresponding with eupnea. When the chemical stimulus increases (as in asphyxia), or when certain excitatory nerve impulses come into play (as in anoxemia), more and more of the respiratory neurons are activated by each excitation wave in the reticular formation until, in severe asphyxia, nearly all the musculature of the body except that of the legs may participate in the respiratory act. A possible explanation for this action of the chemical stimulus is given on page 563.

It is probably more than coincidence that the neurons that have the greatest sensitivity to the chemical stimulus are also the most resistant to inactivation by adverse circumstances such as trauma, oxygen-lack, cyanide poisoning, and depression by narcotic drugs such as morphine, alcohol, barbituric acid derivatives, chloral hydrate, magnesium salts, ether, etc. Thus when the medulla is injured, respiration becomes purely inspiratory (gasping) before it fails and the expiratory mechanism is completely inactivated before inspiration ceases. The same thing is observed when oxygen-lack is produced in the brain by reducing the amount of oxygen in the blood (as by inhalation of an inert gas such as nitrogen or nitrous oxide), or by interfering with the blood supply of the brain, for here also purely inspiratory gasps are seen before respiration ceases and expiration is paralyzed before inspiration. Ascending doses of cyanide (which interferes with tissue oxidations and thus can cause oxygen-lack in the cells of the respiratory center) have an effect of the same nature, and in poisoning by depressant drugs again purely inspiratory efforts are the last to disappear, expiration becoming entirely passive some time before inspiration ceases. The terminal gasps are due to contractions of the diaphragm, and the part of the respiratory center by which this muscle is innervated thus is seen to retain its capacity to function longer than the rest of the respiratory regulating system. As a matter of fact there is one respiratory movement that persists longer than that of the diaphragm, namely, contraction of the muscles of the floor of the mouth.[88] When recovery occurs the same order is followed in the reverse direction. First the muscles of the buccal floor begin to contract, then the diaphragm, and finally the accessory muscles of inspiration and the expiratory group. These facts probably mean that the reticular cells which innervate the depressor muscles of the mandible and the diaphragm are the most primitive and most simply organized and therefore the least vulnerable parts of the respiratory center; the respiratory movements of the buccal floor may well be a survival of the organization for water-breathing in some primitive ancestral form (see page 598).

Pitts and his associates have recently suggested that variations in synaptic resistance within the reticular formation may play a prominent part in the integration of the respiratory act; they believe that the inhibito-inspiratory impulses that are essential to the rhythm of the respiratory center (page 555) owe their effectiveness to an increase produced by them in the resistance to the spread of impulses throughout the inspiratory reticulum, and they suggest that chemical factors (acute hypercapnia,* oxygen lack) may have a similar effect. Gesell, Lapides, and Levin[62] likewise suggest that hypercapnia may interfere with the conduction of afferent excitatory impulses throughout the center. In terms of this

*For the definition of this and related terms, see page 675.

conception, the differences in threshold of the different neurons of the reticular system might be ascribed, not to failure of some of the neurons to respond to an excitation wave sweeping over them, but to failure of the wave to reach them. The resistance in the neurons connected with the muscles of quiet inspiration must then be lower than that in the neurons connected with the expiratory and the accessory inspiratory groups. The latter can be activated either by increasing the strength of the excitation wave or by decreasing the resistance to its spread. Conversely, if by deleterious influences such as trauma, anoxia, or narcosis, synaptic resistance is increased everywhere in the system, the parts in which this is normally high would naturally suffer more than those in which it is low, hence the persistence of diaphragmatic breathing after paralysis of the other respiratory movements under such circumstances. This attractive conception is admittedly hypothetical.

3. Reciprocal Innervation.—When impulses appear in a nerve supplying an inspiratory muscle they disappear from a nerve to an expiratory muscle. This was clearly shown by Bronk and Ferguson[21] in the internal and external intercostals of the cat (Fig. 218), and we may fairly conclude that a similar relation exists between the inspiratory and expiratory muscles as a whole. To accomplish this a part of the discharge from the neurons activating the inspiratory muscles must be carried to those connected with the expiratory group and this part of the inspiratory discharge is expended in inhibiting the activity of the expiratory cells. Conversely, whenever the expiratory neurons discharge impulses some of the discharge reaches the inspiratory cells and inhibits their activity. Thus we can account for the fact that the two antagonistic groups of respiratory muscles are normally activated alternately; they act simultaneously only under the influence of convulsant poisons, which are conspicuous for their ability to abolish reciprocal innervations.

Recent evidence[130] indicates that (at least in the cat) the main function of the "expiratory center" is inhibition of inspiratory activity, for this always occurred when the expiratory cells were stimulated directly (by electrodes inserted into the medulla) though contrac-

Fig. 218.—Discharge of motor impulses in nerves to an internal intercostal muscle (above) and an external intercostal muscle (below). Cat with vagodepressor and carotid sinus nerves cut and with respiratory muscles paralyzed with curara; artificial respiration has been stopped and asphyxia is developing. Note alternation of impulses in the two nerves although no respiratory movements are present. (From Bronk and Ferguson: Am. J. Physiol. **110**: 700, 1935.)

tion of the expiratory muscles often did not ensue. It seems probable that the presence or absence of an active expiratory effort is determined by other factors, among which the strength of the existing chemical stimulus is outstanding: if this is sufficiently great, active expiratory efforts will occur whenever the expiratory cells are released from inhibition, but if it is not, the expiratory discharge will do no more than inhibit the activity of the inspiratory cells. The "expiratory center" is therefore fundamentally an "inhibito-inspiratory center," and a relatively simple conception that is also in accord with existing evidence is that afferent inhibito-inspiratory impulses of all types are transmitted directly to the "expiratory center," from which they spread throughout the system as an inhibito-inspiratory influence; active expiratory efforts will also arise if the existing stimuli (chemical and nervous) to the expiratory neurons are sufficiently strong to activate them when they are thus released from inhibitory control. As noted above (page 556), these relations apparently are not so clean-cut in the dog as in the cat, but the general organization is doubtless the same in all mammals.

The reverse relation—inhibition of expiratory activity during the discharge by the inspiratory cells and incitement of the former by cessation of the latter—has received less attention although there is no doubt of its existence. Perhaps it is for this reason that in some persons, at least, the violent expiratory effort of the cough reflex (which is not under voluntary control) can be minimized or prevented by voluntarily avoiding a deep inspiration, while as soon as the latter is taken a strong expiratory contraction inevitably occurs. Here the deep inspiration, by setting up strong afferent inhibito-inspiratory impulses (see page 573), would abolish the discharge from the inspiratory neurons and thus permit the expiratory group to become active.

As we have seen repeatedly, the interrelationships of these factors in respiratory control are modified at every phase and in almost every respect by chemical influences. The latter will be considered later (page ???) and further discussion of the interplay of the factors concerned in respiratory control will be undertaken in Chapter XL. One additional point deserves attention at this time:

The Way in Which the Respiratory Movements Are Made to Vary by the Nervous Discharge

Studies of action potentials in nerves leading to respiratory muscles have shown that here—as elsewhere in the neuromuscular system—gradations in the degree of muscular activity can be brought about in two different ways. These are: (1) changes in frequency and duration of the discharge in individual motor neurons; (2) variations in the number of motor neurons that participate in each burst of activity. The first of these was shown by Adrian and Bronk[3] to be responsible for changes in strength of contraction in the diaphragm. During quiet breathing they found that individual fibers in the phrenic nerve were carrying impulses at a frequency of about 20-30 per second, which suffices to produce an incomplete tetanus in the muscle fibers innervated by it, but the various units do not work in unison and therefore the diaphragm contracts smoothly. During dyspnea, however, the frequency of the discharge increased

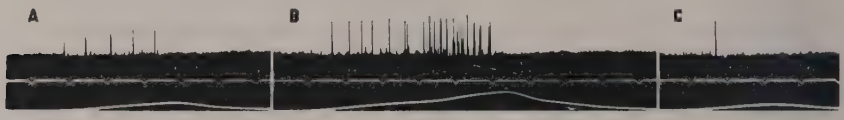


Fig. 219.—Discharge of motor impulses in a nerve twig to an external intercostal muscle of a cat in three successive inspirations of varying depth (indicated by bottom record, which shows thoracic movements). *A*, moderate inspiration; *B*, deep; *C*, shallow. Time in 1/5 second. At *A* there is a short volley of impulses in three fibers; at *B* more neurons are in action, the average frequency of discharge is higher and lasts longer; at *C* there is but a single impulse in each of two fibers. (From Bronk and Ferguson: Am. J. Physiol. **110**: 700, 1935.)

to 50-80 per second, at which rates the muscle fibers innervated by each neuron enter into a complete tetanus and thus the strength of contraction of the diaphragm is increased. These workers could find no evidence that gradations in the strength of contraction of the diaphragm were achieved by variations in the number of active neurons. On the other hand, when Bronk and Ferguson[30] studied the motor discharge to the intercostal muscles it became apparent that here, as in the limb muscles (Chap. X), grading in muscular activity is due to variations in the number of motor neurons participating in the discharge as well as to changes in the frequency and duration of the discharge in individual motor fibers (Fig. 219).

The amount of air moved in and out of the lungs per minute (the minute volume of respiration) is therefore determined by the following factors:

1. The *interval* between successive groups of nerve discharges (outbursts) to the muscles of inspiration (and expiration, if active); this factor of course determines the rate of breathing, while all of the others regulate the depth.

2. The *frequency* of the nerve impulses transmitted by the individual nerve fiber to its motor unit during each inspiratory (or expiratory) discharge.

3. The *duration* of the discharge.

4. The *number of motor units activated* during each inspiration or expiration. This applies not only to the total number of muscles that participate in the act, but also to the proportion of fibers of the individual muscles. In the case of the diaphragm this factor apparently does not operate, but this is the only exception as far as is now known.

Thus in quiet breathing the intervals between the outbursts of nerve impulses producing inspiration are long, the number of muscles that receive impulses is minimal (perhaps only the diaphragm and external intercostals), the number of impulses reaching each contracting fiber at each outburst is low—perhaps only one (see Fig. 219), the duration of the outburst is brief, and even in the contracting muscles (apart from the diaphragm) there are many fibers that are not activated. When dyspnea is produced (Fig. 219) the intervals between the inspiratory outbursts are shortened, more muscles are activated by each, the number of impulses reaching the muscle fibers at each outburst is greater and more—eventually all—of the fibers of each active muscle (except the diaphragm) are made to contract at each outburst.

Gesell and his collaborators[60, 63] have found that the electrical activities of nerves leading to inspiratory muscles are characteristically of the "slowly augmenting" type, in which the discharge increases slowly and ceases abruptly, while the discharge in nerves to expiratory muscles is either of the "rapidly augmenting" type (beginning abruptly and fading away gradually) or else the "steady state" type, in which the activity is periodically maintained at a constant level. These patterns could be followed throughout the medulla and spinal cord and all parts of the inspiratory and expiratory systems were found to have the same electrical characteristics. The abrupt cessation of the inspiratory discharge is in all probability due to the summation of the factors involved in terminating the inspiratory act, viz., diminution in the chemical stimulus by reason of the movement of air in and out of the lungs, relative insensitivity of the inspiratory neurons after they have discharged their volleys of impulses (toppling of an unstable equilibrium into a relatively stable one), and inhibito-inspiratory nerve influences set up by the inspiratory discharge itself (from distention of the lungs, and from the pneumotaxic center). The sudden onset of the expiratory discharge apparently is due to release of the expiratory neurons because of cessation of the activity of the inspiratory neurons by which the expiratory neurons were being held in check, the existing chemical stimulus being strong enough to activate the latter when they are thus released.

THE CHEMICAL STIMULATION OF THE RESPIRATORY CENTER*

By this time in the course of our inquiry into the factors involved in adjusting pulmonary ventilation to the needs of the body we have repeatedly encountered instances of the importance of chemical factors, and before we proceed further it is advisable to have some understanding of the identity of this chemical stimulus and of the way in which it acts. For many years physiologists have believed that the activity of the respiratory center can be adjusted to the metabolic needs of the body by means of any or all of the three main changes in the blood that are characteristic of metabolic activity, i.e., decreased oxygen tension, increased carbon dioxide tension, and increased hydrogen ion concentration, and nothing has happened (or is likely to happen) to alter this belief. But whereas it was assumed until recently that all of these chemical influences act directly upon the respiratory center, and in much the same way, discoveries made during the last few years have shown this not to be the case. The simple conceptions of respiratory control that had previously been entirely

*For the definitions of terms commonly used in this connection, see page 675.

satisfactory therefore are no longer acceptable. The significance of this statement will be evident when the older ideas are viewed in the perspective of the recent discoveries.

Historical.—Ever since the discovery of the importance of oxygen to the maintenance of living processes, physiologists have been impressed with the fact that respiratory activity runs parallel with oxygen consumption. It was natural therefore to conclude that the increased call of the body for oxygen directly provides the stimulus to the respiratory center; this was the view adopted by Rosenthal[135] and widely held for many years. The classical experiments of Haldane and his collaborators,[67, 68] however, showed clearly that the respiratory center of man is too insensitive and variable in its response to oxygen-lack to permit the belief that this factor can be the most important one in respiratory control. Carbon dioxide, on the contrary, exhibited much greater potency and consistency as a respiratory stimulant and the sensitivity of the center to it was so great that this metabolic product came to be regarded quite generally as the agent responsible for respiratory control under normal conditions.* Subsequently, as a result of work in other laboratories and of theoretical considerations concerning the acid-base balance of the blood, Haldane modified his views about the specificity of carbon dioxide as a respiratory regulating agent and accepted the hydrogen ion as the responsible factor; carbon dioxide was then held to act, not as such, but by virtue of the H^+ ions that are dissociated from the carbonic acid formed when CO_2 is dissolved in water (see Nielsen[118] for a critical survey of the literature). This explanation was not wholly satisfactory, however, for it was known from a number of experiments[84, 97] that respiration was stimulated much more intensely by a given change in hydrion concentration in the blood produced by carbon dioxide than by other acids. This discrepancy in turn was accounted for by other experiments which showed that carbon dioxide can penetrate cells more rapidly than most other substances of biological importance (including H^+ ions).

This was well shown in the experiments of Jacobs.[87] He found that young toad tadpoles became entirely inactive within five seconds after immersion in water saturated with CO_2 (pH about 3.8-3.9), while in water containing enough of another acid (hydrochloric, oxalic, formic, salicylic, acetic, butyric) to produce the same hydrion concentration, they remained active for thirty minutes or more. Even when the solution of CO_2 was made almost neutral (pH 6.9) with bicarbonate the effect on the animals was the same as that of the unbuffered solution, showing that it was neither the hydrion concentration nor the HCO_3^- ion that was responsible. Similar results were obtained with various motile protozoa (Coleps, Paramecium, Colpidium), and in these it was possible to see evidence that the CO_2 had penetrated rapidly to the interior of the cell and was acting "in a sense from within outward"; the body began to swell almost immediately, the contractile vacuoles became paralyzed, and even signs of coagulation of the protoplasm appeared before the cilia were paralyzed. When the organisms were placed in other acids, the cilia were paralyzed before the internal structures were affected. Jacobs was also able to show that CO_2 can penetrate cells more readily than bicarbonate by using a flower *(Symphytum peregrinum)* which is pink in acid solution, blue in alkaline; when one of these flowers was immersed in distilled water (pH 5-6) the blue color remained unchanged, but when one was placed in a solution of CO_2 in $\frac{M}{2}$ $NaHCO_3$ (pH 7.4) it promptly became pink.

As a result of these events the belief that the hydrogen ion concentration is the common denominator in the chemical control of respiration came to be very widely held. There were numerous discrepancies between pulmonary ventilation and the hydrion concentration of the arterial blood (see Gesell[57, 58]) but these could be explained satisfactorily by making the very reasonable assumption that it is the hydrion concentration within the center that determines its activity, and that this concentration need not always be in equilibrium with that in the arterial blood. Thus Winterstein[168] explained the hyperpnea of anoxemia as being due to accumulation of acid products of incomplete oxidation within the cells of the center—a *centrogenous* hyperpnea, in contrast with that produced by inhalation of carbon dioxide, which elicits a *hematogenous* hyperpnea. Gesell[57] adopted this conception and carried it to its logical conclusion, viz., that the chemical control of breathing is always due to the hydrion concentration within the cells of the center and that this is determined by an equilibrium

*As we shall see (page 587) oxygen-lack is now known to owe its stimulant effects to reflexes aroused in the carotid and aortic bodies, not to a direct effect on the respiratory center.

among three factors: (1) the chemical stimulant content (carbon dioxide and other acid-forming metabolic products) of the arterial blood, diffusion of these occurring from blood into center if the content of the former is higher than that of the latter, and conversely; (2) the rate at which the same sort of chemical stimulant material is produced within the cells of the center by their own metabolism; (3) the efficiency of the blood supply of the center in relation to its metabolism, for this must determine the extent to which acid-forming substances produced in these cells are permitted to accumulate within them. The same conception has recently been extended[59] to include the regulation of the activity of the reflexes aroused by chemical agents, and with the addition of the latter factor an all-inclusive and satisfactory conception of respiratory control seemed to have been attained.

Recently in the course of a series of investigations in Krogh's laboratory of the physiology of muscular exercise, evidence has been obtained which leads Krogh[95] to conclude that carbon dioxide has specific effects in the control of breathing and does not act solely by virtue of its acid-forming properties. This conclusion is derived from carefully done experiments on trained human subjects who showed in response to carbon dioxide inhalation an intense hyperpnea with little change in arterial pH, whereas ingestion of ammonium chloride (see page 646) led to considerably greater changes in arterial pH with little or no hyperpnea.[118] Thus, in one subject inhalation of air containing CO_2 (4 per cent) caused an increase of 10 liters per minute in pulmonary ventilation associated with a change in acidity represented by a decrease of pH 0.04-0.045 in the arterial blood; with ammonium chloride the drop in arterial pH amounted to 0.08, while the increase in pulmonary ventilation was only 0.3 liter per minute. In another subject CO_2 inhalation increased pulmonary ventilation 10 liters per minute with a decrease in arterial pH of 0.02; during the period of ammonium chloride ingestion arterial pH fluctuated from 0.08 below to 0.08 above the resting level while pulmonary ventilation remained practically constant. The acidosis observations were made during "steady states" extending over periods as long as 10 days, so that it is inconceivable that the differences between the effects of the hydrogen ion and of carbon dioxide could have been due to failure of the cells of the respiratory center to come to equilibrium with the arterial blood with respect to hydrogen ions. Nielsen[118] discusses the literature on this subject and gives reasons (which seem to the writer to be more than adequate) for concluding that the chemical stimulus to the respiratory center cannot be the hydrogen ion but is carbon dioxide acting as such.

Thus we come back to the view first held by Haldane and his collaborators as far as the specificity of carbon dioxide is concerned, but with two important differences. The first is that we can no longer regard the response of the respiratory center to its stimulus as a physiological constant (as Haldane did) but must make provision for marked variations in the amount of respiratory activity to be expected from a given amount of the chemical stimulus (see page 568). The second is that changes in hydrion concentration of the arterial blood are now known to be capable of setting up reflexes (in the carotid and aortic bodies—see page 588) that are strongly stimulant to the respiratory center.

At this point, having identified the chemical stimulus to the respiratory center as carbon dioxide, our next step will be to attempt to explain its effects on that structure. The reader should understand that such an attempt involves numerous assumptions which, although justified, in the writer's opinion, by existing information, are none the less assumptions.

THE MODE OF ACTION OF CARBON DIOXIDE ON THE RESPIRATORY CENTER

In the foreword to this section (page 534) we saw that living structures in general are able to carry on their functional activities only because of the continuous liberation and utilization of energy, and that nerve cells (such as those of the respiratory center) are just as subject to this rule as structures by which measurable work is being done. Warburg[161] suggested some years ago that this is because the energy used by nerve cells is expended in bringing about and maintaining the organization requisite for their functioning (i.e., the maintenance of normal permeability relations, keeping apart cell constituents that otherwise would mix, etc.). This suggestion is in complete harmony with the recent trends of cellular biochemistry (e.g., the "dynamic protoplasm" of Peters[127] and the intracellular phenomena held by Clark[36] to be responsible for the actions of drugs).

The significance of these statements may be appreciated if we picture a nerve cell (or an integrated group of them, such as the respiratory center) as corresponding with a modern city. There will be activities of various sorts, but they can be divided into two main categories: (1) The *specialized functions,* represented in the city by the daily activities of the clerks, artisans, storekeepers, salesfolk, professional people, shoppers, students, teachers, visitors, etc., whose movings to and fro furnish the most highly developed, most specialized, and most obvious manifestation of the state of well-being of the community; in nerve cells the corresponding specialized function is the initiation, reception, and transmission of nerve impulses, in muscle cells it is contraction, in gland cells secretion, and so on. (2) The *maintenance functions,* represented in the community by provision and maintenance of transportation facilities, of supplies of food, water, and energy (coal, gas, oil, gasoline, electricity), of police and fire protection, of removal of ashes, trash, and garbage, etc.; in living cells this corresponds with the functions that may be called vegetative because they serve to keep the cell alive and capable of carrying out its specialized activities.

The citizens of a community as a rule do not realize how much energy must be devoted merely to maintaining the organization upon or through which they can continue to carry out their special activities; it is only when something happens to interfere with these maintenance functions (a heavy snowfall, a flood, a disastrous fire, a violent strike, a breakdown in a major source of supply of water or power, an earthquake, or—in these days—a war) that their importance for the well-being of the community is made evident; conversely, experience has shown that conspicuously successful performance of the specialized functions by the citizens of a community follows automatically when the maintenance functions are carried out with unusual efficiency. The situation in a living cell presents striking analogies: one can estimate the extent of vegetative activities and their importance to the performance of specialized functions only by observing what happens when the former are interfered with, and it is highly probable that the specialized functions follow more or less automatically when the ashes of previous activities are removed, when the materials necessary for renewed activity are furnished, and when the organization upon which these and other intracellular phenomena can take place is kept from disintegrating.

All this is accomplished by these vegetative or maintenance reactions. It is probably fair to look upon the performance of the specialized function of a cell as the result of the toppling of an unstable equilibrium into a relatively stable one; to bring about the instability requisite for another burst of activity, according to the Second Law of Thermodynamics[19] energy must be expended, but once this has been done the performance of the specialized function can proceed automatically. Thus the vegetative or maintenance reactions, though less spectacular than the specialized ones, are actually responsible for the latter. Furthermore (other things being equal), the more energy that is made available the more rapidly will the requisite instability be attained.

We can carry this general conception over to the neurons of the respiratory center with no essential change: the discharge of impulses by them depends upon an adequate supply of oxidizable (food) material and of oxygen. They have, however, become specialized in two respects which account for their peculiar place in the organization of the body. One is their

connection with the respiratory muscles in such a way that their integrated activity is responsible for the body's entire gas exchange with the environment. The other is their sensitivity to changes in the tension of carbon dioxide within their cells (which, in view of the ready diffusibility of this gas, is practically the same as that in the arterial blood and alveolar air under all physiological conditions), the relation being such that an increase in carbon dioxide tension causes an increase in the rate and vigor of their discharge and conversely. An increase in the tension of carbon dioxide on or in the respiratory neurons means an increase in the number of molecules of the gas within them (page 616). If we view these molecules as foreign chemicals (i.e., drugs) we may conclude that the CO_2 molecules enter into the dynamic system within the respiratory neurons in such a way as to accelerate their energy-yielding (oxidative) reactions; this makes their biochemical equilibria more unstable and increases their excitability. To carry further the analogy between such a cell and a community, we can liken this effect with the manner in which the movement of traffic can be expedited by a few policemen stationed at strategic points, the implication being that the action of CO_2 now under consideration is a selective or specific one, depending upon combination of relatively few molecules of the substance with specialized parts of the cell protoplasm in such a way as to increase the functional activity of the entire system. This is in contrast with the nonselective or diffuse narcotic action which high concentrations of carbon dioxide can exert upon nerve tissue in general and which (as we shall see below) can also be exerted upon the respiratory neurons if the number of molecules is sufficiently great.

By means of the hypothesis under discussion the influence of carbon dioxide on the respiratory center can be accounted for in terms that are in line with recent trends of thought. The first effect of an increase in the carbon dioxide tension in the reticular system is to increase the depth of inspiration, which is accomplished by a longer, more vigorous discharge over the nerves to the muscles of quiet inspiration and an increase in the number of neurons that participate in the activity (page 556); an increase in the rate at which instability is created in these neurons could account for this because the instability would then be greater at the time of discharge than had previously been the case. Further increase in the carbon dioxide tension brings into play more and more muscles that had not participated in respiration previously, which means a corresponding involvement of additional reticular neurons in the discharge until, at the maximal effect, all of them respond to each excitation wave in the reticular formation. This also can be accounted for by increasing excitability (instability) of the neurons by reason of the presence of more CO_2 molecules within them. Whether we should hold that the excitation wave always sweeps over the entire reticular formation and that only those cells respond in which the existing instability is sufficiently great, or that the resistance to the propagation of the wave is so great that the number of cells reached by it depends directly on the strength of the original discharge, cannot be decided by existing evidence, but the choice makes no essential difference as far as the general conception is concerned. These questions are considered more fully in Chapter XLI.

No consideration of the action of carbon dioxide on the nerve cells would be complete without some mention of its depressant or narcotic properties, which have been known for many years, investigated repeatedly,[169] and actually utilized to produce surgical anesthesia in man.[99] The action responsible for this is probably quite unlike that underlying the stimulant effects of the gas on the respiratory neurons. The current tendency[36] is to attribute a narcotic action such as this to a nonspecific blanketing of catalytically active cell surfaces by a chemically indifferent substance which thus interferes with intracellular oxidative processes (and therefore with specialized functions) much as a snowstorm interferes with the activities of a community.

From these considerations it is evident that the action of carbon dioxide on the neurons of the respiratory center is a dual one:—a stimulant effect from low concentrations, due to incorporation of CO_2 molecules into the cell organization in some specific manner so as to enhance intracellular oxidations, and a nonspecific depressant or narcotic effect from much larger amounts. A stimulant effect from small doses of many narcotic substances is a long-familiar observation (see[169] for literature) and is frequently called the *excitement state of narcosis.* Perhaps the stimulant effect of carbon dioxide on the respiratory neurons is only a special example of this, but the analogy must certainly be qualified, because in the case of carbon dioxide acting on the respiratory center the excitement stage is relatively much stronger and it extends over a much wider range of concentration than is true of this substance acting on nerve cells elsewhere or of other narcotic agents acting on the respiratory center. Perhaps (on an evolutionary basis) when changes in environment calling for transition from water-breathing to air-breathing took place, only those animals could survive in which the central respiratory regulating system had these peculiar characteristics, for the respiratory centers of fishes are for the most part relatively insensitive to the stimulant effects of carbon dioxide (Krogh[95]). It is noteworthy that the stimulant effects of carbon dioxide will be manifested only if the neurons are in good condition and the concentration of the gas is not too high. When the concentration is increased pulmonary ventilation reaches a maximum at about 9 per cent carbon dioxide in the inspired air and further increases lead to a diminution in respiratory minute volume.[119] These results were obtained in normal men with maximally sensitive respiratory centers, so that the power of carbon dioxide to depress these neurons (as any others) is readily demonstrable. When the respiratory neurons are not normal but are depressed by various agencies, their ability to be stimulated by carbon dioxide is reduced although their ability to be depressed by it is not (see page 672); depressant effects can always be elicited by carbon dioxide if the concentration is high enough, whether stimulation occurs or not.

THE SENSITIVITY OF THE RESPIRATORY CENTER TO CARBON DIOXIDE

Ordinary air contains only negligible amounts of carbon dioxide, but if this gas is added to the inspired air respiration is stimulated and the volume of air breathed per minute is increased. The smallest change in carbon dioxide to which the human respiratory center normally responds is extremely small: Campbell, Douglas, Haldane, and Hobson[33] found that an increase of 0.22 vols. per cent in the carbon dioxide content of the alveolar air was enough to double the alveolar ventilation in one of their subjects, and a decrease of the same extent below the resting level caused apnea. This corresponds with a change of 1.5 mm. in the tension of CO_2 in the alveolar air. The average of all their observations gave the figure of 0.3 per cent for the increase in alveolar CO_2 required to double the volume of alveolar ventilation, and Haldane[66] states that one-twentieth of this is enough to produce distinct effects on breathing. This gives an accurate picture of the sensitivity of the respiratory center because, in view of the ready diffusibility of carbon dioxide, the tension to which the center is exposed (that of arterial blood) is equal to that in the alveolar air. The response to small changes in the carbon dioxide tension of the blood is due en-

tirely to the center, not to reflexes from the carotid and aortic bodies; the sensitivity of these structures to carbon dioxide, as far as is now known, is decidedly less than that of the center (page 589).

The increase in pulmonary ventilation produced by increased carbon dioxide content in the inspired air is proportional to the latter up to a certain point (about 9 per cent—Nielsen) and then diminishes; this is probably a manifestation of the narcotic effect of carbon dioxide in high concentration. It is noteworthy that the hyperpnea produced by carbon dioxide, vigorous as it appears to be, is by no means maximal. In Nielsen's experiments the maximum pulmonary ventilation that could be produced in athletic subjects by inhalation of air enriched with carbon dioxide was about 50-60 liters per minute whereas the same subjects had no difficulty in breathing 110-120 liters per minute when they were exercising vigorously. Attempts at bringing the ventilation to the latter point by increasing the CO_2 content of the air inhaled when not exercising led only to a diminution in ventilation. Barcroft and Margaria[18] also found that the increase in pulmonary ventilation produced by exercise was about double that obtainable by inhalation of carbon dioxide; yet the subjects were distinctly more uncomfortable during the dyspnea of CO_2 than during that of exercise. The significance of these observations will be taken up later (page 604). At present we need note only that carbon dioxide, while highly effective as a stimulant to the respiratory neurons, has definite limitations in that respect.

THE INFLUENCE OF THE OXYGEN CONTENT OF THE INSPIRED AIR

Haldane and Priestley[68] found that respiration in their subjects was not stimulated when the oxygen content of the inspired air was reduced until it had fallen to about 13 per cent, at which point hyperpnea occurred. Subsequent workers, however, have placed the threshold considerably lower than this, Ellis[52] in particular finding that respiration began to be stimulated in 21 out of 29 healthy young men when the oxygen of the inspired air was reduced only to about 18 per cent on the average. The lowest altitude at which the hyperpnea associated with ascent in an airplane has been observed to occur is about 4000 feet;[8] this corresponds with inhalation of 18 per cent oxygen at sea level. The opinion has been widely held that oxygen-lack tends to increase the rate of breathing and not the depth, but this now seems not to be the case. Observations on aviators, who are normal subjects in an environment abnormally low in oxygen (see Chapter XLV), show clearly that the depth is increased primarily and preponderantly, effects on the rate being inconstant and relatively slight.[8] The effects of CO_2 and anoxemia on respiration are additive.[47a] In animal experiments chemoreceptor reflexes which, as we shall see in Chapter XL, are responsible for the stimulant effects of oxygen-lack on respiration, typically cause an increase in depth of breathing first, an acceleration only when the stimulus is an unusually strong one. For these reasons it seems fair to conclude that the rapid shallow breathing formerly believed to be due to anoxemia *per se* was actually due to adventitious circumstances. All observers agree that the hyperpnea produced by oxygen-lack is much more variable among different individuals than that elicited by increased carbon dioxide; this is true not only of the minimum effective amount of anoxemia but also of the strength of the response. The hyperpnea of oxygen-lack is typically much less intense than that of CO_2 ex-

cess, for the volume of breathing is seldom more than doubled by the former while with the latter four- or five-fold increases are common. Many subjects show no hyperpnea from oxygen-lack until the oxygen of the inspired air has fallen to 12 per cent or less and some show none at all. Cyanosis appears when the oxygen falls below 10 per cent and when it gets as low as 8 per cent unconsciousness and collapse are likely to occur.

The reasons for the relative weakness of anoxemia as a respiratory stimulant are as follows: Anoxemia produces hyperpnea by means of chemoreceptor reflexes (page 587). At the same time it decreases the capacity of the central neurons to carry on their functions, and it does this in at least three different ways: (1) it interferes with the "maintenance reactions" in the cells of the center by reducing the number of molecules of oxygen available for the purpose; (2) it reduces the carbon dioxide tension in the arterial blood because of the increased pulmonary ventilation produced reflexly, and this, by reducing the number of molecules of CO_2 within the neurons, tends to diminish their activity; (3) it causes constriction of cerebral blood vessels because it reduces the arterial CO_2 tension and the dilator effect of CO_2 upon them is the main if not the sole factor in maintaining these vessels in a normal state (page 607). Thus there is good reason to suspect that although respiration can be stimulated reflexly by oxygen-lack, this has the characteristics of a pathological rather than a physiological type of control, and we shall have abundant reason to verify that suspicion later.

Ordinarily an increase in the percentage of oxygen in the inspired air does not depress breathing unless oxygen-lack was present before the oxygen was added. In fact the breathing of normal persons may be stimulated when they breathe air enriched with oxygen. In the presence of oxygen-lack the situation is different, for addition of oxygen to the inspired air will then reduce or abolish the chemoreceptor reflexes that had been driving respiration and the latter will be depressed accordingly. This is especially evident in diseases in which anoxemia is present (page 691), but it is also seen in normal persons exercising to the limit of their tolerance. Under the latter circumstances Nielsen[120] found that on raising the oxygen content of the inspired air to 45-47 per cent the alveolar ventilation was reduced, the volume of oxygen absorbed was augmented, and the capacity for violent exertion was increased; he attributed these results partly to the decreased muscular effort involved in respiration, partly to improvement in the capacity of the heart to function at the higher tension of oxygen. It may be recalled that the superb showing of the Japanese swimmers at the Olympic Games in 1934 was attributed (whether justly or unjustly) to their having employed oxygen inhalations beforehand. The various effects of inhalation of oxygen are considered in more detail in Chap. XLVI.*

THE INFLUENCE OF HYDRION CONCENTRATION

When acid is added to the blood it is promptly neutralized by alkali withdrawn mainly from combination with CO_2 as bicarbonate (see Chap. XLIII). The result is to increase the amount of CO_2 in physical solution in the blood, which increases its tension and thus leads to diffusion of the gas from the blood into

*Several investigators[83, 82] have recently reported depression of the respiration of anesthetized animals on breathing air enriched with oxygen and have assumed such results to be representative of the normal state in man, which is clearly not true. The reason for this discrepancy may lie in species variations or in artificialities of the experimental conditions; the anesthetic used by these workers (chloralose) has properties that may dominate the results obtained in experiments like these (page 581).

the tissues. In the respiratory center this means more molecules of CO_2 and therefore more active respiration, which will continue until, by elimination of CO_2 from the lungs, the state of affairs in the center is restored to normal; the acid-base balance of the blood will then strike an equilibrium at a new level. If alkali is added instead of acid, corresponding changes occur in the reverse direction: carbon dioxide molecules at first diffuse from the respiratory neurons into the blood because the CO_2 tension of the blood was lowered by the alkali, and breathing is depressed accordingly, but this is counterbalanced by accumulation of CO_2 because of reduced pulmonary ventilation. Thus it is possible to account for respiratory effects from acid or alkali through their effects on the tension of carbon dioxide in the respiratory center.

In certain types of acidosis in man (as in diabetes) there is, however, often enough hyperpnea to reduce the alveolar and arterial CO_2 tension to as little as a half or even a fourth of normal. This must mean that the respiratory center is being stimulated by something other than CO_2, for otherwise the hyperpnea would cease as soon as the CO_2 tension had been restored to normal. Until recently such a result would have been attributed to a direct stimulation of the respiratory neurons by hydrogen ions. The respiratory center was supposed to be so sensitive to the hydrogen ion that breathing would be markedly stimulated by increases in hydrion concentration too small to be detected by existing methods. Thus Haldane[67] (p. 185) calculated that the 1.5 mm. increase in arterial CO_2 tension that sufficed to double pulmonary ventilation in one of his subjects (see page 564) would mean a fall of only 0.012 in arterial pH (a change that is not detectible with certainty by any of the methods now in use) and that one-twentieth of this (a drop of pH 0.0006) would be enough to affect breathing quite definitely. As we have already seen (page 561), the careful experiments of Nielsen have shown clearly that the respiratory center of man is not nearly as sensitive to changes in hydrion concentration as this implies and have cast serious doubts upon the ability of the hydrogen ion per se to stimulate the center directly. It would seem that if the central neurons are directly affected by changes in hydrion concentration their sensitivity to that stimulus must vary enormously from time to time.

It is possible that the hyperpnea of acidosis (in so far as it cannot be ascribed to an increase in carbon dioxide tension in the center) is due entirely to reflexes from the carotid and aortic bodies, for these have recently (1939) been found to be aroused by changes in pH well within the limits that might be encountered clinically (page 588). Nielsen[118] found that the sensitivity of the respiratory center (estimated by its response to inhalation of 4 per cent carbon dioxide in air) was definitely increased in his subjects by acidosis. His conclusion was that the hyperpnea of acidosis is the result of the increased excitability of the center. Perhaps the increased excitability of the center noted by Nielsen is partly or even entirely due to the reflexes just alluded to. This would make it similar to the hyperpnea of anoxemia, which Nielsen (as well as many others) believed also to be due to increased excitability of the center to carbon dioxide, and which, as we shall see (page 587), is almost certainly due to reflexes from the carotid and aortic bodies. On the other hand, it is by no means certain that the respiratory neurons do not respond directly to changes in hydrion concentration, as they were for many years believed to do. The writer is following Krogh,[95] whose experience and wisdom in matters pertaining to respiration are preeminent, in believing that the center responds to carbon dioxide as such and not to the hydrogen ion, but this does not preclude all sensitivity to the latter. The subject needs reinvestigation in the light of these recent developments.

We arrive at the following conception of the chemical control of respiration: *Carbon dioxide—a normal product of aerobic metabolism, possessing the*

unique properties of being able to diffuse very readily through living membranes and of being excitant in low concentrations and depressant (narcotic) in larger amounts—is responsible for the regulation under all ordinary circumstances. It acts as such and not by virtue of the formation of carbonic acid and liberation from this of hydrogen ions. The number of CO_2 molecules within each cell of the center determines its activity (probably through some still obscure drug action that facilitates the oxidative or maintenance reactions within the cell) and this number is determined by the tension of the gas in the arterial blood (which is in equilibrium with that of the alveolar air). Reflexes from the carotid and aortic bodies may become strong enough to drive the center during asphyxia, anoxemia, or acidosis (page 594) and when this occurs the result is the same as though the center had become more sensitive to carbon dioxide. Actual changes in sensitivity probably occur however: in hibernation (in which breathing is very slow and shallow although blood CO_2 content is very high and blood acidity as great as pH 7.1[128]*) some such change is very evident, and it is probable that an equally marked but opposite change occurs during exercise, though this may be because of the impingement of a new or augmented nerve influence upon the reticular formation (see page 604). Whether chemical factors affect breathing by altering the resistance to conduction across synapses in the reticular formation (as suggested by Pitts) or by altering the excitability of the neurons of that formation, remains to be determined.*

CHAPTER XL

THE REFLEX REGULATION OF RESPIRATION

We have seen (page 556) that, according to recent investigations, the respiratory center does not act rhythmically because of some quality conferred upon it by chemical stimuli (as had been generally believed to be true), but is enabled to do so only because of nerve impulses which rhythmically exert an inhibitory effect upon it. This in itself is enough to indicate the importance of the reflex factor in respiratory control. Further evidence in that direction is the recent discovery that certain chemical factors (notably oxygen-lack and acid-excess), which for many years had been supposed to stimulate breathing by a direct effect upon the respiratory center, actually produce their effect by setting up stimulant reflexes from the carotid and aortic bodies (page 587). Finally, the fact that the most vigorous hyperpnea of which man is capable—that due to muscular exercise—is associated with no increase in any known chemical factor in the blood but is nevertheless much stronger than any hyperpnea that can be elicited simply by intentionally increasing the chemical stimulus (page 604), practically compels the conclusion that nervous factors are dominant over biochemical in respiratory control. These points have been alluded to more or less incidentally in the preceding chapter. It is now necessary to consider them more specifically.

According to information now available the most important reflex influences in respiratory control are those aroused in the lungs by their alternate inflation and deflation, and those which originate in the carotid and aortic reflex zones. These two are the only sets of reflexes that are known to be essential to the automatic control of pulmonary ventilation; as long as they are operating respiration retains its normal character and adaptability, but when either is removed the breathing suffers in some important respect. If Stella and Pitts are correct, the impulses carried to and from the pontine pneumotaxic center (page 555) deserve inclusion with those from the lungs as an essential factor in respiratory control. Other afferent impulses can also affect breathing; some of these effects are either incidental and seemingly purposeless (such as the respiratory effects of emotional disturbances, or of strong visual, auditory or tactile sensations) or else they are protective devices (such as the suspension of breathing during irritation of the nasal and pharyngeal endings of the trigeminal nerve, or the effort at expulsion of an irritant from the air passages by means of a cough or a sneeze). Afferent impulses are also undoubtedly aroused in the thoracic walls and the respiratory muscles, but there is as yet no compelling evidence that they play any essential part in the control of breathing. Reflexes from the muscles and tendons probably cause the hyperpnea of exercise (page 604).

RESPIRATORY REFLEXES FROM THE LUNGS (THE HERING-BREUER REFLEXES)

These are the reflexes set up by inflation and emptying of the lungs, first described by Hering and Breuer in 1868.[78] The afferent pathway is in the vagus; this fact was also discovered by Hering and Breuer, who thus called

attention for the first time to the importance of the vagus in the control of respiration. This subject was thoroughly explored by Head[73] who devised a method for recording contractions of a slip of the diaphragm in such a way that only active contractions of the muscle were recorded and it was possible to inflate and deflate the lungs without producing passive disturbances in the record. This can be done readily in the rabbit, though not in other laboratory animals.

Head found that when he occluded the trachea just at the end of a normal inspiration, the diaphragm relaxed and apnea resulted until the increasing asphyxia overcame the nervous inhibition; then an inspiratory effort ensued, but it differed from the normal movements in that it was more powerful and lasted longer (Fig. 220). When the trachea was closed at the end of expiration an inspiration followed at the normal time, but it was abnormally powerful and prolonged (Fig. 220). Evidently the degree of inflation of the lung produced by a normal inspiration is sufficient to inhibit the contraction of the diaphragm. When the lungs were artificially inflated to a greater extent than this a prolonged inhibition of the diaphragm ensued (Fig. 221), and the result was the same when hydrogen was used for the inflation, showing that over-ventilation of the

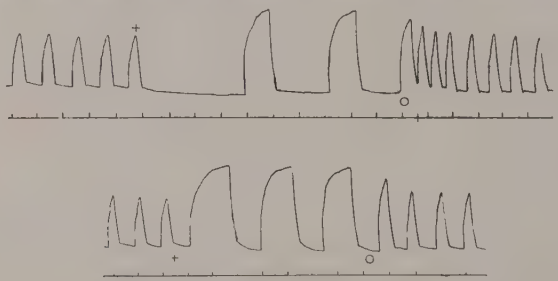


Fig. 220.—Hering-Breuer reflexes. Contraction of an isolated slip of the diaphragm (Head's method) in a rabbit.

Upper record:—occlusion of trachea (+) at end of a normal inspiration; note prolonged relaxation of the diaphragm, broken by two unusually marked and prolonged contractions; tracheal obstruction removed at (o).

Lower record:—occlusion of trachea (+) at end of a normal expiration: there is no pause, but succeeding inspiratory efforts are greatly increased in strength and duration; obstruction removed at (o). (From Head: J. Physiol. **10**: 1, 1889.)

alveoli was not responsible. If the lungs were made to collapse by allowing air to enter the chest, or by sucking air out of the trachea, the diaphragm underwent a prolonged tonic contraction (Fig. 221). By suction of air out of the lungs after a quiet inspiration it was possible to induce an inspiratory movement long before it would have occurred otherwise. All these phenomena were abolished when the vagus nerves were frozen, thus preventing them from carrying the essential afferent impulses. Breathing then became slower and the chest tended to assume the inspiratory position; after a time respiration became deeper again, but it continued to show inspiratory pauses and it remained slow (Fig. 222).

These results showed clearly, as indeed Hering and Breuer had already demonstrated, that inflation of the lungs inhibits inspiration and that collapse of the lungs stimulates it. This is the essence of the self-regulation (Selbststeuerung) of respiration by means of the vagus.

Since Head's time many other investigations have been made along these lines, but little of real importance was added to our knowledge about the influence of the vagus on respiration until quite recently. Stimulation of the central end of a cut vagus was employed by many workers as a means for determining the influence of the nerve on respiration, but the results were conflicting. As more is learned about the factors involved in such experiments it becomes increasingly evident that results of general applicability could never be obtained in that way. For one thing, it is now clear that the vagus trunk of a dog or cat contains at least three sets of nerve fibers that are capable of affecting respiration powerfully, these being: (1) the fibers mediating the two Hering-Breuer reflexes; (2) those representing the

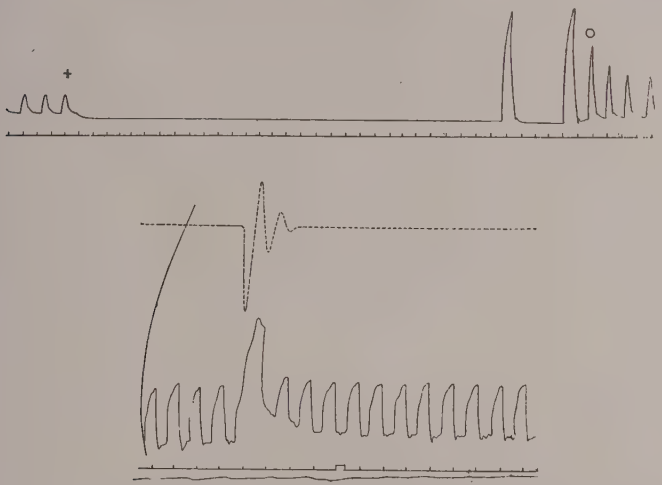


Fig. 221.—Hering-Breuer reflexes. Contraction of slip of diaphragm of rabbit as influenced by excessive inflation of lungs (upper record, + indicating inflation, o release) and by collapse of lungs (lower record, suction of air out of trachea at end of expiration, dotted line indicating change in intratracheal pressure). (From Head: J. Physiol. **10**: 1, 1889.)

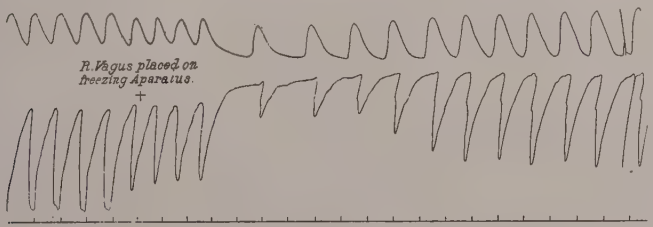


Fig. 222.—Effect of section of vagus nerve on respiration. Contractions of slip of diaphragm of rabbit (lower record) and changes in intratracheal pressure (upper record). Right vagus frozen (and thus inactivated without irritation); + indicates when nerve was placed on freezing apparatus. The left vagus had already been frozen. (From Head: J. Physiol. **10**: 1, 1889.)

sensory innervation of the trachea and bronchi, irritation of which causes a cough or at least active expiration; (3) the afferent fibers from the arch of the aorta and aortic body, stimulation of which may cause either inhibition of breathing and fall in blood pressure or hyperpnea and rise in blood pressure, depending upon the predominance of fibers from the pressoreceptors of the aortic arch or from the chemoreceptors of the aortic body (see page 569). Furthermore, differences in depth and type of anesthesia can greatly modify the results: under ether anesthesia it is very difficult to elicit respiratory inhibition in the

dog by stimulation of the vagus (or indeed of any afferent nerve), while under chloralose it is extremely easy to do so. Differences in the type of the stimulus may also modify the result; Hammouda and Wilson[69] noted that faradic current of a given strength when applied to a vagus of a dog at a rate of 50 per second caused apnea, but at a rate of 10 per second it caused acceleration of breathing. Differences in strength of the stimulus have long been known to have marked influence on the result. In the dog or cat fully (but not too deeply) anesthetized with chloralose or a barbiturate the tendency, in the writer's experience, is for the weakest effective stimulus to produce a decrease in breathing (either in rate or depth or both); a stronger current is likely to elicit expiratory contractions and may increase the rate of breathing; a very strong stimulus is again likely to be inhibitory. These results suggest that the inhibito-inspiratory (Hering-Breuer) fibers have the lowest threshold, the excito-inspiratory (Hering-Breuer) fibers the next (perhaps the fibers of the cough reflex also), while the fibers from the pressoreceptors of the aortic arch have the highest threshold and usually are dominant over the fibers from the chemoreceptors of the aortic body. It is obvious that the possibilities for obtaining useful results by electrical stimulation of a system as complicated and variable as this are poor indeed.

Recently new light has been cast on this subject, particularly by the work of Adrian,[2] who succeeded in reducing the vagus of the cat to a few fibers or even a single fiber carrying impulses from the lungs. By studying the action potentials in nerves thus simplified he was able to confirm most of Head's results and to add other data which now (in conjunction with the recent work of Pitts et al.) make it possible to form a reasonably clear picture of the part played by the Hering-Breuer reflexes in the control of respiration. This is as follows:—

The impulses are, of course, afferent.* They affect the inspiratory neurons predominantly and under ordinary circumstances perhaps exclusively. It may be that inspiration is inhibited by one set of impulses because they activate the "expiratory center" primarily (see page 557), but it is none the less fair to regard all of the important respiratory effects of these reflexes as being exerted on the inspiratory phase. Two distinct sets of nerve impulses are involved, one aroused by inflation of the lungs (inspiration), the other by deflation (expiration). The impulses aroused by inflation inhibit the inspiratory cells of the center, those aroused by deflation excite them. The inhibitory discharge occurs at every inspiration, and when the lungs are maintained in the inflated condition this discharge is continuous, showing that the receptors from which it arises are of the slowly adapting type. The excitatory discharge in the expiratory phase apparently does not occur during quiet breathing, but only when the lungs are emptied to a greater extent than under resting conditions; this can be accomplished in the experimental animal by pressure on the chest, by suction of air out of the trachea, or by pneumothorax, and probably also by active contraction of the expiratory muscles.† The receptors from which the impulses arise are located in the most distensible parts of the lungs, probably in the alveolar ducts (see page 547); the stimulus to the receptors is stretching. There are two sets of receptors, one for the inhibitory discharge,

*The only efferent fibers carried by the vagus to the respiratory structures below the larynx are those of the motor (constrictor) innervation of the bronchial muscle and possibly secretory fibers to the mucous glands of the bronchial passages. These are not directly concerned in the control of respiration, and the function of the vagus in this respect is entirely dependent upon afferent impulses carried by it to the respiratory neurons in the central nervous system.

†In Adrian's experiments there was probably more sustained activity of inspiration throughout the expiratory phase than is usual, for this is especially likely to occur in cats under chloralose anesthesia. One consequence of this would be less deflation of the lungs than normally. Adrian's conclusion—that the excito-inspiratory impulses are not set up under physiological conditions—may therefore be subject to modification. It is difficult to account for all of the Hering-Breuer phenomena on a basis of inhibito-inspiratory reflexes alone.

the other for the excitatory. The receptors are practically insensitive to changes in the composition of the air and are unaffected by air currents; their function is to signal the state of inflation of the lungs and nothing else. The inhibito-inspiratory receptors are the ones that normally keep the center informed about the volume of the lungs, and they are operative under all normal conditions. The excito-inspiratory receptors are brought into action only when deflation of the lungs is greater than it is under resting conditions.

The way in which the inhibito-inspiratory impulses affect breathing appears to be as follows: The many receptors from which they arise have different sensitivities to stretching; some are so sensitive that during quiet breathing they may continue to discharge impulses throughout the expiratory phase, and during inspiration the resulting inflation increases only the frequency of their discharge; others are inactive during expiration but their discharge begins with the onset of pulmonary expansion and becomes progressively more rapid until inspiration reaches its peak; others are still less sensitive to stretching, their activity beginning only at greater degrees of inflation. As a result of this organization, the inspiratory neurons of the center, as soon as they begin to discharge impulses to the inspiratory muscles, are subjected to an afferent influence which tends to stop their activity, and the degree of this inhibition is directly proportional to the degree of their activity (i.e., the depth of inspiration). The general arrangement is the same as that encountered elsewhere in the body (e.g., in the cardiovascular system) in that Nature seems to have developed an apparatus which is prone to overexert itself and which can survive only when this tendency is continually opposed. These inhibito-inspiratory impulses from stretch receptors in the lungs are the counterpart in the respiratory system of the impulses which are aroused by intravascular pressure in the carotid sinuses and aortic arch and which are indispensable to the normal control of blood pressure and heart rate (page 462).

On this basis it is easy to see why the inhibito-inspiratory impulses should check inspiration and thus lead to a smooth transition to expiration without a pause, but that (according to Adrian) is only a part of their function. They probably can also help to accelerate breathing, particularly when an increase in ventilation is needed, and the way they can do this is not as obvious as the above. According to Adrian, the nature of the effect of such impulses on the central neurons will depend upon whether the neurons are themselves discharging impulses or resting when the afferent inhibitory influence reaches them: in the former case the discharge will be curtailed and the resting period of the neurons will ensue more rapidly than it would otherwise, while in the latter case the same afferent influence will interfere with the processes of restitution. In the first case the expenditure of "active material" during the phase of activity would be diminished by the inhibitory influence and the interval required in preparation for a fresh burst of activity would be shortened; the rate of breathing, other things being equal, would therefore increase while the strength of each discharge to the respiratory muscles would not be diminished because the discharge preceded the inhibition. In the second case, however, an inhibitory influence upon the processes transpiring within nerve cells when they are not discharging impulses would delay removal of the ashes of previous activity and interfere with the building up of the state of unstable equilib-

rium requisite for a new burst of activity; the interval required for such processes would therefore be increased and the rate of breathing would be slowed (Fig. 223).

This general conception of a conserving and facilitating influence by inhibitory nerve impulses reaching an "all-or-none" tissue during its phase of activity, and of the opposite type of influence by the same impulses reaching the same tissue during its resting phase, has much to recommend it, and probably possesses wide applicability. It should be pointed out, however, that Adrian also concluded that the excito-inspiratory Hering-Breuer reflex is not a factor under ordinary circumstances, but this conclusion is by no means universally accepted, and further investigation is desirable to determine whether other animals or other anesthetics would make a difference in the results obtained. At present it seems to the writer that although only the inhibitory reflex is important during quiet breathing, the excitatory one can be brought into play by active contractions of the expiratory muscles. Thus during dyspnea both the factor postulated by Adrian and the additional one of direct excitation would cooperate to increase the rate of breathing. The way in which these factors cooperate with others in the normal control of breathing will be considered later.

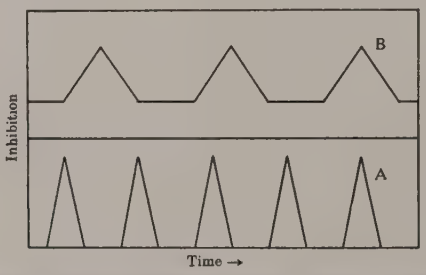


Fig. 223.—Diagram of Adrian's conception of the influence of afferent inhibitory vagus impulses on the rate of respiration. Abscissa = time; ordinate = number of inhibitory impulses per unit time. *A*, rapid development of high degree of inhibition with inspiration, none during expiration: this causes rapid breathing. *B*, slow increase in inhibition with inspiration, persistence of considerable inhibition during expiration: this causes slow breathing. (From Adrian: J. Physiol. 79: 332, 1933.)

When the vagus nerves are cut breathing characteristically becomes slower and deeper, the chest tends to assume a position of partial inspiration, and often there are pauses at the end of inspiration as well as expiration. In time, however, these effects tend to diminish; even in an hour or so in an acute experiment an animal's breathing may become normal again after vagotomy and it may show a normal type of increase in rate and depth when CO_2 is inhaled. Whether this means that other afferent impulses (notably the inhibito-inspiratory and excito-expiratory impulses from the pneumotaxic center, which also wax and wane in the rhythm of respiration) can completely take over the duties of the Hering-Breuer reflexes, is unknown. If the vagi are cut above the origin of the recurrent laryngeal nerves most of the muscles of the larynx will be paralyzed and the glottis will not open during inspiration as it normally does. This may interfere with the passage of air in and out of the lungs and tend to slow the breathing, but it is not a prominent factor. A tracheotomized animal shows practically the same respiratory effects as a normal one from

section of the vagus nerves. The dangers of vagotomy lie more in the abolition of the cough reflex, because of interruption of its afferent side, than in anything else.

RESPIRATORY REFLEXES FROM THE AORTA AND CAROTIDS

The Hering-Breuer reflexes undoubtedly play a large part in regulating the rate and depth of breathing under all ordinary circumstances, and this is readily understandable because they originate in receptors that are activated by the movements of the lungs. We now have to consider a set of respiratory reflexes which arise, not in the respiratory system, but in specialized receptors in close relation with the walls of certain major blood vessels—a location in which one scarcely expects to find elements of importance in the control of respiration. These are the afferent impulses from the stretch receptors (pressoreceptors) of the aortic arch and carotid sinuses, the importance of which in the control of blood pressure and heart rate has already been discussed (Chapter XXXIII), and from chemically sensitive nerve structures (chemoreceptors) located in the carotid and aortic bodies. The discovery of these reflexes —particularly those from the chemoreceptors—undoubtedly was one of the great events in respiratory physiology in recent years. The first of these to be discovered were the reflexes from the aortic region; this was done by J. F. and C. Heymans[82] in 1927. Almost simultaneously Danielopolu and his collaborators,[46] stimulated by the recent discovery of carotid sinus circulatory reflexes by H. E. Hering, reported reflexes from the carotid region similar in the main to those described by Heymans and Heymans in the aorta. C. Heymans and his collaborators, to satisfy themselves on these points, then began a series of experiments on carotid reflexes,[79-81] with the result not only of confirming the observations of Hering and of Danielopolu, but also of extending and adding to them so greatly as to constitute practically a new discovery, for which Heymans was awarded the Nobel Prize in Physiology for 1938. The results obtained by Heymans and his associates have been confirmed in the main by a number of different workers, but since this entire subject has developed in less than ten years it is not surprising that final answers to a number of the questions that were raised by his work are not yet available and that there should be some difference of opinion about several points of fundamental importance.

A brief summary of the undisputed facts about these reflexes is as follows: The respiratory reflexes arising in the aortic region are carried to the respiratory center by both *depressor* (aortic, Cyon) nerves, those arising in the carotids by both *sinus* (intercarotid, Hering) nerves. Reflexes originating in one of these regions are qualitatively identical with those from the other. The respiratory reflexes from the carotids are exaggerated by section of the depressor nerves and conversely; this is also true of the circulatory reflexes. Inactivation of one pair of these nerves may reduce but it will not abolish the respiratory effects of these reflexes in the intact animal. In the recent furore over carotid reflexes there has been a tendency to overlook this point and some of the discrepancies recorded in the literature are due to the mistaken assumption that all of the reflexes now under consideration emanate from the carotid reflex zone. The respiratory reflexes originating in each of these zones consist of two sets, one governed by pressure, the other by chemical influences, and

the effects of stimulation by these two means on the respiratory center (as on other medullary functions) are exactly opposite. *The receptors from which the pressure reflexes arise are anatomically distinct from those responsive to chemical changes, for the former are located in the adventitial coat of the carotid sinuses and aortic arch while the latter are localized in the carotid and aortic bodies. The pressure-sensitive receptors are unaffected by chemical factors and the chemosensitive receptors are unaffected by pressure changes.* The impulses from the two sets of receptors in each reflex zone are, however, carried over the*

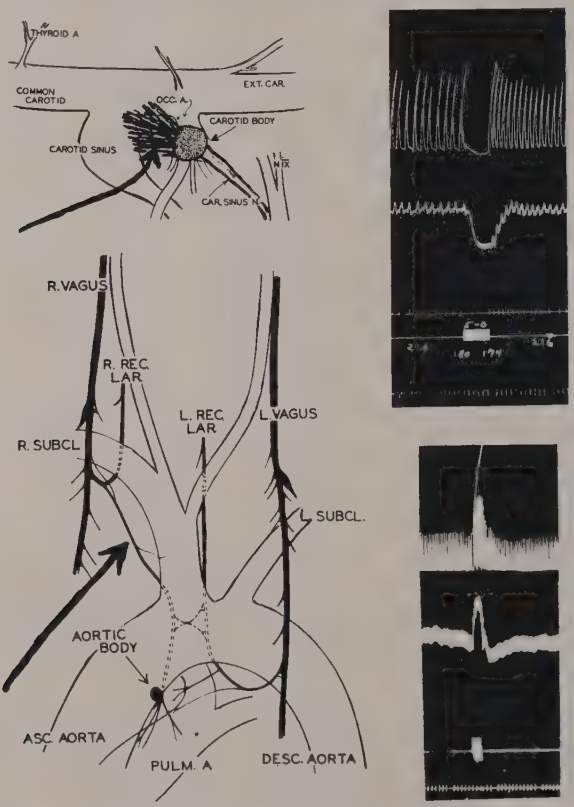


Fig. 224.—Effects of electrical stimulation of nerves from pressoreceptors and chemoreceptors in the dog.

Upper: Stimulation of fibers from pressoreceptors of carotid sinus at position indicated by arrow (between carotid sinus and carotid body). Tracing shows (from above down) respiration, arterial blood pressure, volume of expired air (in 500 ml.), signal, time in 5 second intervals. Note apnea, fall in blood pressure, and slowing of the heart (from 210 to 180-174) though both vagodepressor nerves were cut.

Lower: Stimulation of fibers from aortic body at point indicated by arrow (before they join other aortic afferents in region of left recurrent laryngeal nerve). Tracing arranged as above (record of volume of expired air omitted here). Note hyperpnea and rise in blood pressure though the vagodepressor nerves were intact. (Carotid reflex zones were denervated.) (From Schmidt: Anesthesia & Analgesia, **19**: 261, 1940.)

*Because of technical difficulties this has so far been proved only in the dog, but it is most probable that the anatomically similar structures in other animals have a similar specialization.

same nerve (sinus or depressor), section of which completely abolishes all reflex activity in that region.

Fig. 224 is a diagram of the various receptors and their innervation in the dog; it shows the points at which it is possible to stimulate nerve fibers carrying impulses from pressure receptors only (in the space between the carotid sinus and the carotid body) or from chemoreceptors only (between the aortic body and the junction of this nerve with the aortic trunk in the region of the right recurrent laryngeal). Typical results of faradic stimulation of these two nerves are also shown in Fig. 224. *It is evident that the effect of impulses from the pressure receptors on the respiratory center is inhibitory; since these impulses are also inhibitory to the vasomotor center one is justified in regarding them as characteristically depressant to medullary functions in general.* Stimulation of the nerve from the chemoreceptors, on the other hand, causes an increase of respiration and blood pressure; impulses from these structures may be regarded as stimulant to medullary functions in general.†* In fact in some instances strong stimulation of the chemoreceptors has been found to cause generalized motor activity throughout the central nervous system, even culminating in generalized convulsions, and these could be abolished instantly by removing the stimulus from the chemoreceptors.[138, 140]

Results similar to these have been obtained by a number of different investigators using more physiological stimuli. There can be no doubt that since the effects exerted on respiration by the two types of reflexes are in general exactly opposed and the stimuli which arouse them are totally different, the parts played by them in respiratory control must also be dissimilar.

Respiratory Reflexes From the Pressoreceptors in the Carotid Sinuses and Aortic Arch

As we have seen, these responses parallel the vasomotor reflexes: rise in pressure in the aorta or carotids tends reflexly to slow breathing and to lower the blood pressure, while fall in pressure in the same regions tends reflexly to increase both respiration and blood pressure. This can be shown conclusively by means of suitable crossed-circulation or perfusion experiments in which it is possible to alter at will the pressure in one of the reflex zones. Fig. 225 shows the results of such an experiment in the aortic region and Fig. 226 represents an analogous experiment on the carotid sinuses. In such cases rise in intravascular pressure regularly causes respiratory inhibition, and this is proved to be entirely reflex in origin because it no longer occurs after section or blocking of the corresponding nerves (aortic or sinus). Stimulation of respiration and circulation may occur when these inhibitory influences are suddenly withdrawn, either by reducing an abnormally high intravascular pressure (Fig. 226) or by denervating all of the reflex zones (Fig. 227), but stimulant effects from the pressure receptors always mean this negative type of stimulation, which is in sharp contrast with the positive stimulant influence

*It is true that these impulses also cause *increased* activity of the cardioinhibitory center but this may mean that their primary effect on the circulatory regulating centers is to inhibit the sympathetic parts of this system and thus, through a reciprocal innervation, to release the cardioinhibitory center from inhibitory control previously exerted on it by impulses from the cardioaccelerator center. Thus all of their effects could be attributed to a depression of medullary activity, but at present this is entirely hypothetical.

†Here the cardioinhibitory mechanism participates in the general medullary stimulation; at least this is true of the carotid body receptors of the dog, for intense reflex bradycardia occurs when they are strongly stimulated chemically.

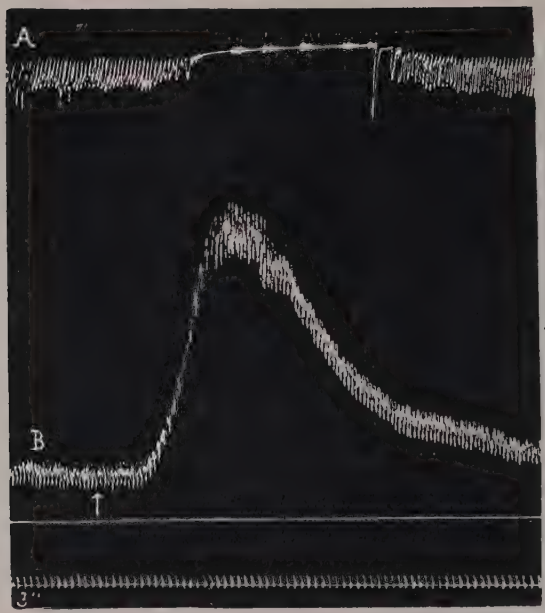


Fig. 225.—Reflex apnea due to rise in pressure in aorta. Dog: Respiratory movements (*A*) are movements of larynx of recipient animal whose head is completely separated from its trunk except for the vagodepressor nerves; the head is supplied with blood from a donor animal. Adrenalin injected into femoral vein of recipient dog; it could not affect movements of the head of this animal except through reflexes carried by the vagodepressor nerves. Blood pressure (*B*) in femoral artery of recipient dog. (From J. F. and C. Heymans: Arch. Internat. de Pharm. et Ther. **33**: 273, 1927.)

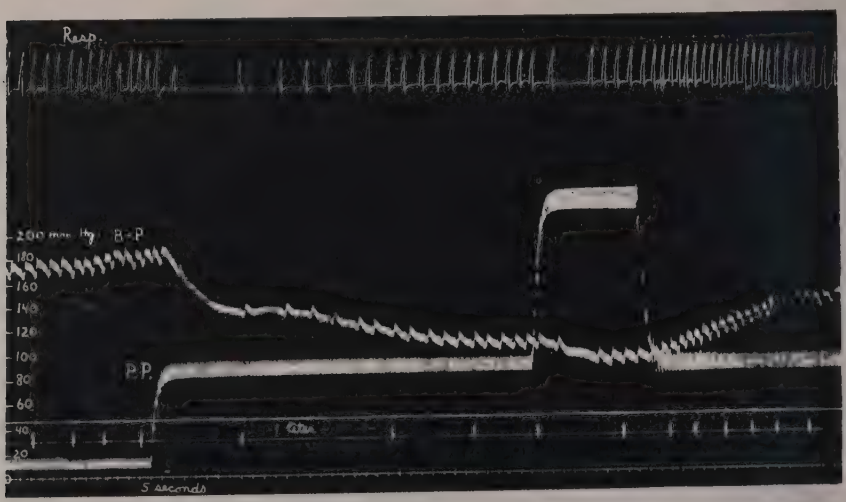


Fig. 226.—Reflex apnea due to rise in pressure in carotid sinuses. Perfusion of both sinuses of dog under barbital narcosis, vagodepressor nerves cut. Blood of donor (*A*) passes through carotids of recipient (*B*) without entering systemic circulation of *B*, since all branches of the carotids are tied. Effects of changes in pressure in carotids of *B* are due entirely to reflexes. *B-P* = blood pressure of recipient (*B*); *P.P.* = pressure in carotids of *B*; pressures recorded by mercury manometers, zero at time tracing, scale of pressure shown at left. Signal line shows volume of air breathed by dog (*B*), each mark representing 1 liter. (From Schmidt: Am. J. Physiol. **102**: 94, 1932.)

of the chemoreceptors. Furthermore, the hyperpnea which follows removal of pressoreceptor activity does not approach in intensity that which occurs when the chemoreceptors are stimulated.

Having thus identified these reflexes and learned the general nature of the effects which they can exert, we come to the question of their importance in the control of respiration. There can be no doubt that this is slight at best, and for practical purposes it is probably non-existent. The chief rôle of the reflexes from the pressoreceptors is to regulate blood pressure by inhibiting vasomotor activity and heart rate when arterial pressure tends to rise, by reducing these depressor influences when the pressure tends to fall; the respiratory effects are probably manifestations of a now useless survival in an air-breathing animal of an organization that may have had considerable importance in a water-breathing ancestral form (see page 598). Thus although prolonged or permanent hypertension ensues when the pressoreceptors are suddenly denervated, hyperpnea, when it occurs at all, is

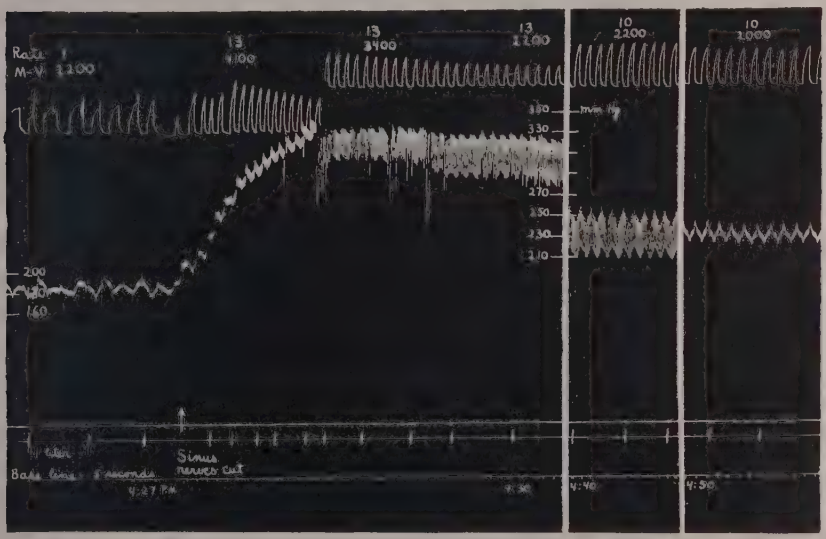


Fig. 227.—Effect of acute denervation of carotid sinuses and aorta. Dog: barbital narcosis; vagodepressor nerves cut. Sinus nerves divided at ↑. Note rise in blood pressure (scale shown) and increase in rate and depth of breathing (shown as Rate and M-V); cardiac arrhythmias also appeared. Subsequent tracings follow ten and twenty minutes later; respiration has recovered from the acute effects of the denervation but blood pressure remains high (about 240 mm.). (From Schmidt: Am. J. Physiol. **102**: 119, 1932.)

transitory (Fig. 227), as though any continuous inhibitory influence by these reflexes on the respiratory center could readily be dispensed with; this is definitely not the case with the vasomotor and cardioregulatory centers. The same conclusion can be derived from perfusion experiments: the changes in blood pressure produced reflexly by alterations in intracarotid and intraaortic pressure are proportional to, and last as long as the latter, but the respiratory effects are responses to a *change* in pressure rather than to any given pressure level and it is characteristic of them that they diminish or disappear when the pressure is maintained at the new point (Fig. 226). Some investigators have claimed that these pressure reflexes exert upon the respiratory center a tonic inhibitory influence comparable with that which they exert upon the vasomotor center, but this seems scarcely justified by existing evidence.

It has also been claimed that these reflexes are solely responsible for the respiratory effects of sudden changes in blood pressure. For many years it has been known that, in

laboratory animals suitably prepared, a sudden rise in blood pressure typically causes respiratory depression or, in favorable subjects, apnea (Fig. 228), and that a fall in pressure may elicit distinct hyperpnea (Fig. 229). Effects such as those shown in Fig. 228 have no clinical importance because the respiratory changes associated with abrupt increases in blood pressure in conscious subjects are dominated by psychic factors and are quite unlike those seen in anesthetized laboratory animals. The analogous effects of sudden marked decreases in blood pressure are so many and complex that the part played by one reflex influence cannot possibly be identified. The theoretical significance of these reactions is, however, considerable because we are dealing here with the relative importance of the two factors (nervous and chemical) which regulate the activity of nerve cells in

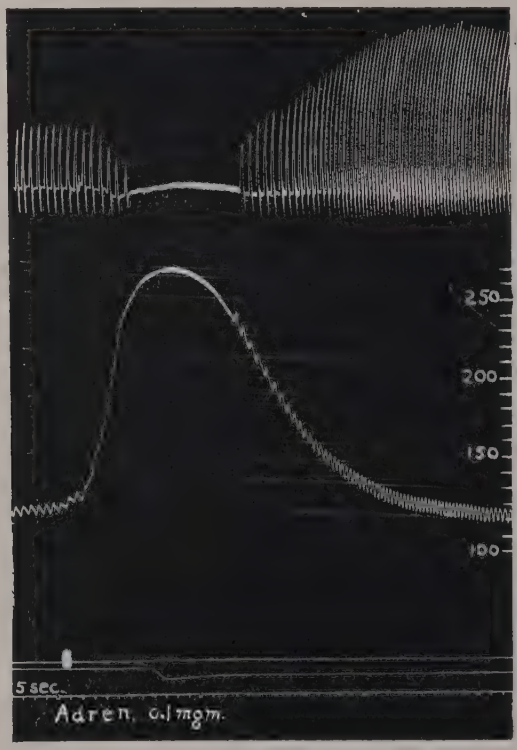


Fig. 228.—Respiratory depression (apnea) due to rise in blood pressure produced by adrenalin. Dog, barbital narcosis.

general, and this is one of the most important questions in all physiology. There is no doubt that reflexes from the pressoreceptors play a part, and probably a large one, in the respiratory effects of sudden changes in blood pressure in anesthetized or decerebrate animals and that previous to the work of Heymans this factor was entirely overlooked by physiologists. However, there is also no doubt that the reflexes are not the sole factor. Thus in animals whose sinus and depressor nerves have been cut drugs which raise blood pressure (as adrenalin) can still depress breathing and drugs which lower pressure can still stimulate it (Fig. 230). It is true that after the nerves are cut the respiratory effects of changes in blood pressure are decidedly less consistent than before (the reasons for this being still unknown), but the fact that respiration is affected at all indicates that some factor or factors other than these reflexes must be concerned. As far as we know at

present, the most important non-reflex factor is change in blood supply of the respiratory center, and this has been shown to be capable of influencing the activity of the center entirely apart from any known reflexes (Figs. 230 and 231). If the same sort of thing occurs in the intact animal (and there is no reason to believe that it does not) we must conclude that a change in blood pressure brings into simultaneous operation two factors which affect respiration in the same direction, and the end-result is the sum of their respective influences. These factors are reflexes from the pressure receptors of the carotids and aorta, and changes in the carbon dioxide tension within the cells of the respiratory center as a result of changes in their blood supply (see page 560). The extent to which the respiratory response to a change in blood pressure is due to either of these influences seems to depend largely on the conditions of the experiment and one factor of particular importance is the anesthetic. Since this raises a question which must always be taken into account in evaluating experimental results, namely, the validity of generalizations drawn from results obtained under one particular set of experimental conditions, it may be worth the reader's while to consider how the choice of the anesthetic can influence the results of experiments such as these.

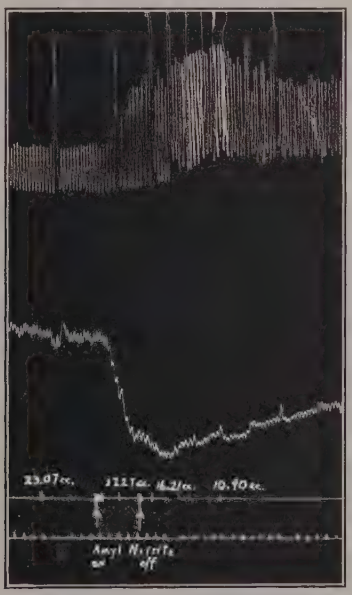


Fig. 229.—Respiratory stimulation due to fall in arterial pressure produced by amyl nitrite. Cat: barbital narcosis; vagus and sinus nerves intact. Figures above signal tracing indicate cerebral blood flow (venous outflow) in cubic centimeters per minute.

For experiments on carotid reflexes chloralose has come to be the preferred anesthetic because blood pressure then is higher and reflexes more active than is the case with other narcotics. This is true of both pressure and chemical reflex systems and it is only fair to point out that current ideas about these reflexes are bound up as intimately with the pharmacology of chloralose as the cholinergic conception of transmission of the nerve impulse is bound up with the pharmacology of eserine or prostigmine. Something is known about the latter but what chloralose does to the central nervous system in general and to these reflex systems in particular is quite unknown. This drug is unlike most of the so-called "indifferent narcotics" in that it can be injected rapidly into a vein without (as a rule) lowering blood pressure, and that spinal reflexes are definitely exaggerated by it; apparently it does not strongly narcotize the heart or the spinal cord and is not therefore an indifferent narcotic in the usual sense of the term. In decerebrate dogs and cats it can

be shown that chloralose frequently increases the sensitivity and the effectiveness of the carotid chemoreflex system;[139] a comparable effect on the pressoreceptors can also be demonstrated though less consistently. At the same time the effects of chemical influences directly on the cells of the center can be shown (by means of inhalations of carbon dioxide) to be diminished and occasionally they are practically abolished although the sensitivity and effectiveness of the chemoreflex system are greater than before. (This means, not that this anesthetic has depressed medullary functions less than most other drugs [which is the reason usually advanced for preferring it], but that it definitely exaggerates these reflex influences.) It is probable that under the influence of this drug breathing is influenced and maintained by reflexes to a greater extent than under any other anesthetic. At the same time blood pressure is high, perhaps abnormally so, and the cerebral blood vessels apparently are dilated by chloralose as by any narcotic; consequently the blood supply of the center is increased. But the metabolic activity of brain cells is decreased by narcotics in general, and there is no reason to regard chloralose as exceptional in this respect; the blood

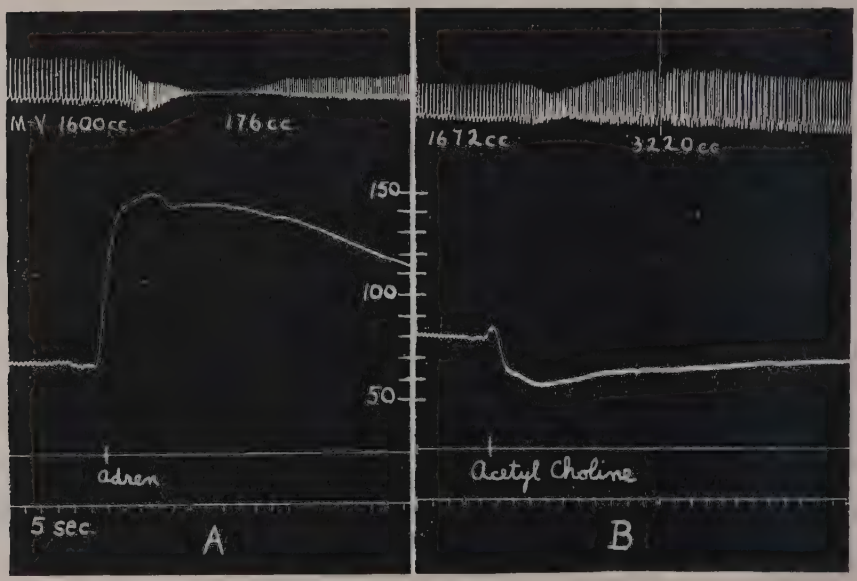


Fig. 230.—Respiratory effects of changes in blood pressure in an animal with depressor and sinus nerves cut. Rabbit: barbital narcosis. *A*, 0.05 mg. adrenalin intravenously; *B*, 0.005 mg. acetylcholine intravenously. Changes in minute volume of respiration: in *A*, from 1600 to 176 ml.; in *B*, from 1672 to 3220 c.c. (From Schmidt: Am. J. Physiol. **102**: 119, 1932.)

flow required to satisfy the needs of the cells of the center for a supply of oxygen and for removal of carbon dioxide would therefore be less than before. Since cerebral blood flow is actually increased by chloralose, the result is that the blood supply of the center is now out of all proportion to its requirements. Putting all these factors together—exaggeration of reflexes, reduced sensitivity to chemical influences, and excessive blood supply of the center—we find a situation in which the influence of alterations in cerebral blood flow is bound to be less important than that of reflexes, and experiments on animals under chloralose therefore give a distorted picture of the relative importance of the reflex and blood flow factors. Other anesthetics which do not exaggerate reflexes (as the barbiturates in dogs[139]), and do not cause an abnormally high blood pressure, obviate this difficulty to some extent, but even then the cerebral vessels are dilated and the metabolism of nerve cells is reduced, so that the blood supply of the center is probably in excess of its needs. In experiments in which the brain is artificially perfused (Fig. 231) the blood supply of the center can be

adjusted so that it is adequate but not excessive, and under such circumstances respiration responds to slight alterations in cerebral blood flow without the intervention of known reflexes. Even then the sensitivity is probably much less than that of the normal unnarcotized center.

It follows that the respiratory effects of changes in blood pressure are not due entirely to reflexes from the carotid and aortic pressoreceptors, as some have claimed.

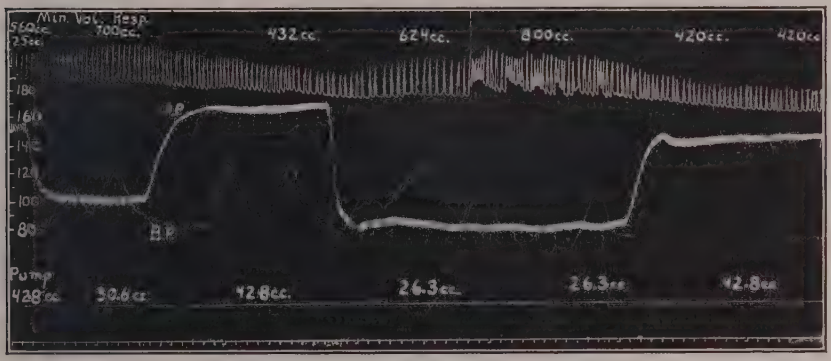


Fig. 231.—Respiratory effects of changes in cerebral blood flow after section of sinus and depressor nerves. Rabbit: anesthetized with barbital and heparinized; depressor and sinus nerves cut; respiration recorded by plethysmograph (minute volume given at top of tracing); blood pressure recorded from subclavian artery (*B.P.*); time in 5 second intervals. Cerebral circulation supplied with blood drawn from a subclavian artery and pumped through the internal carotids, both vertebral arteries being closed; *PP*, perfusion pressure; *Pump*, volume of blood pumped (per minute) through the brain. Note that respiration is depressed by an increase and stimulated by a decrease in cerebral blood flow.

Fig. 232.—Effects of external pressure on carotid sinus. Dog: chloralose anesthesia, depressor nerves cut, both sinus nerves intact. Left sinus compressed between thumb and finger at signal. Note fall in blood pressure and apnea.

Another claim for the importance of these reflexes is that they may be responsible for some cases of sudden respiratory failure during anesthesia with nitrous oxide. Downs[48] compiled a series of these unfortunate occurrences in man and adduced some experimental

evidence to indicate that under nitrous oxide-oxygen anesthesia the carotid pressoreceptors are abnormally sensitive to external pressure. He suggested that some sudden and unexplained fatalities under nitrous oxide-oxygen anesthesia might be due to mechanical stimulation of these receptors, either by operative manipulations in the region or by pressure by the thumbs of the anesthetist behind the angle of the jaw. The fall in blood pressure and inhibition of breathing that normally follow stimulation of these receptors might, he believes, be exaggerated sufficiently to cause death. It is true that the position of the pressoreceptors in the adventitial coat of the carotid sinus is such as to make them accessible to external pressure (Fig. 232) but it is probable that the most important factor in fatalities under nitrous oxide anesthesia is damage to the central nervous system by prolonged anoxemia (see Chapter XLV). Impulses from the pressoreceptors might well aggravate the situation by causing a fall in blood pressure, thus reducing further an already deficient oxygen supply to the central neurons and causing sudden and perhaps permanent failure of breathing.

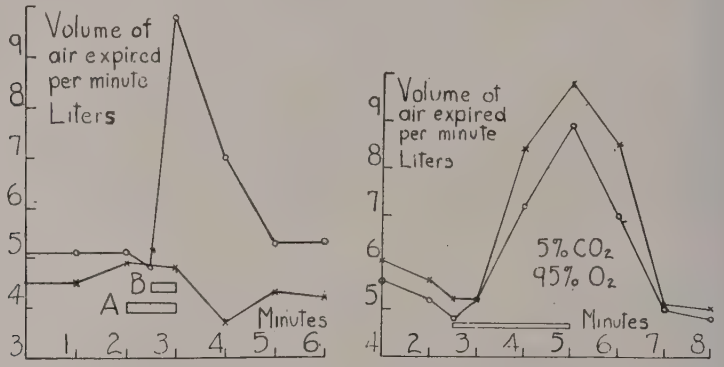


Fig. 233.—Effect of denervation of carotid sinuses on respiratory response of unanesthetized dog to inhalation of nitrogen and CO_2. Both experiments on the same animal.

On left:—nitrogen inhalation, —o— before denervation, —x— after denervation; *B*, duration of inhalation (thirty seconds) before denervation; *A*, duration of inhalation (one minute) after denervation. Note complete absence of respiratory response after denervation.

On right:—inhalation of 5 per cent CO_2 in oxygen for two and a half minutes, —o— before denervation, —x— after denervation. There is no significant difference after the denervation. (From Gemmill and Reeves: Am. J. Physiol. **105**: 487, 1933.)

RESPIRATORY REFLEXES FROM THE CHEMORECEPTORS

Impulses aroused in the carotid and aortic bodies by chemical agents are undoubtedly of fundamental importance to the control of respiration, and of much greater importance to this than to the control of the circulation; in both respects they are in sharp contrast with reflexes from the pressoreceptors. The chemoreceptors are activated by increase in the carbon dioxide tension or hydrion concentration or decrease in the oxygen tension in the fluid bathing them, and since these are precisely the blood changes which physiologists have for many years associated with the chemical control of respiration, it is not difficult to see why the discovery of these reflexes has necessitated considerable revision in respiratory physiology. Furthermore a number of drugs and poisons (lobeline, nicotine, cyanides, sulfides), which have long been known to stimulate breathing, have been found to owe these effects entirely to stimulation of the chemoreceptors and not—as previously supposed—of the respiratory center itself; thus a considerable amount of revision has been necessary in pharmacology. The reflex nature of these effects has been demonstrated in two general ways: first, by showing that they occur when the corresponding nerves

are intact but not when they are cut or otherwise inactivated (Fig. 233); second, by eliciting them in perfusion or crossed circulation experiments in which the exciting agents could act only on the carotid or aortic reflex zone and had no contact with other parts of the reacting animal (Fig. 234). In tests of the actions of drugs a variation of the first method was to inject a minute dose directly into the carotid or aorta so that the drug reached the corresponding chemoreceptors immediately and in concentration high enough to affect them but was ineffective elsewhere (Fig. 235). Still another variation was to use action potentials in the sinus nerve as the criterion of chemoreceptor activity.

The results obtained with these methods by various investigators have completely confirmed the observations originally made by Heymans and his collaborators in so far as the existence and general character of these reflexes are

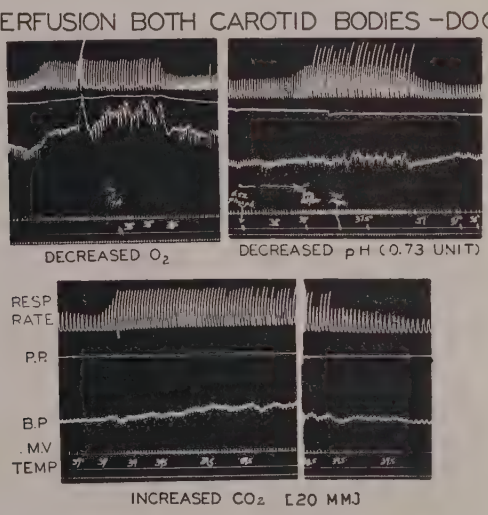


Fig. 234.—Carotid body reflexes in perfusion experiments.

Perfusion of both carotid bodies of dogs with modified Locke's solution. Each tracing shows (from above down) respiration (pneumogram), perfusion pressure (*PP*), femoral blood pressure (*BP*), volume of expired air (in 500 ml.), temperature of perfusing fluid, time in 5 second intervals. Vagodepressor nerves were cut in each case.

Decreased O_2-solution buffered with bicarbonate and CO_2 to pH 7.4 and freed of oxygen by bubbling nitrogen through it.

Decreased pH—solutions contained phosphate buffers—pH 7.25 and 6.52 respectively, both saturated with oxygen and free of CO_2.

Increased CO_2—solutions buffered with bicarbonate to pH 7.4 in both cases, CO_2 tension 0 and 20 mm. respectively. (All pH readings at 38° C.).

concerned. There is, however, some difference of opinion about their physiological significance. To obviate confusion in the reader's mind, it appears to be proper to give a conception of the physiological significance of these reflexes that seems to the writer to furnish the best fit with the available facts, while indicating, wherever that can be done, the points upon which opinions differ and the reasons therefor. The reader who is especially interested will find divergent opinions expressed in three recent review articles on the subject.[59, 80, 140]

The Part Played by Chemoreceptor Reflexes in the Control of Respiration.—It is generally agreed that the chemoreceptors can be stimulated by any or all of the three main chemical changes that occur in the blood during asphyxia or as the result of increased metabolic activity, i.e., decreased oxygen tension, increased carbon dioxide tension, and increased acidity. It is also generally agreed that at least one of these—carbon dioxide—acts upon the central neurons at the same time and in the same direction as on the chemoreceptors, and until recently it was almost universally believed that this is equally true of the other two factors. Consequently a change in respiratory activity associated with a change of any of these factors in the arterial blood might be due exclusively either to chemoreceptor reflexes, or to a direct effect on the center, or to some combination of the two. There are no distinguishing characteristics which enable one to decide which of the two influences is at work; the hyperpnea produced by chemoreceptor reflexes looks exactly like that due to

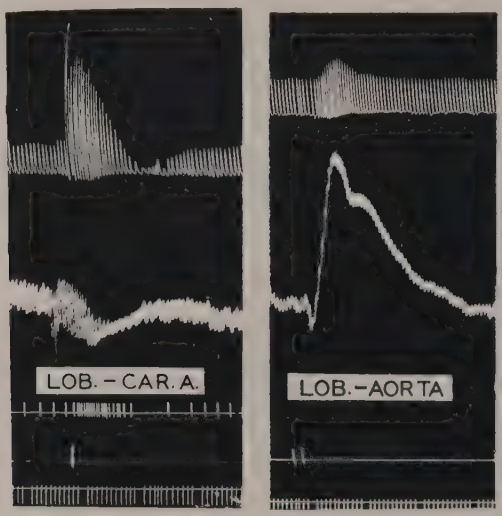


Fig. 235.—Chemoreceptor reflexes from intraarterial injections.

Experiments on dogs. Each tracing shows pneumogram (above), arterial blood pressure, and time in 5 second intervals; the one on the left also shows respiratory minute volume (in 500 ml.).

Left—all nerves intact; lobeline (0.1 mg.) injected into one common carotid through a needle tied into its superior thyroid branch: note hyperpnea (intense), bradycardia, and hypotension.

Right—carotid reflex zones denervated, vagodepressor nerves intact; lobeline (0.2 mg.) injected into aorta through small catheter whose tip lay just central to source of vessel supplying aortic body; note hyperpnea (relatively slight) and hypertension.

direct stimulation of the central neurons, for in each case an increase in depth of breathing is the characteristic result. Whatever differences there are between reflex and central responses to these factors must therefore be quantitative, having to do with such things as the relative sensitivity, power, speed of reaction, and ability to withstand adverse circumstances. The differences of opinion about the physiological significance of chemoreceptor reflexes arise from different interpretations of the validity of the experimental evidence.[140] In perusing the literature on this subject the reader will do well to remember

that the points to be decided are quantitative, not qualitative; much of the current confusion is due to the drawing of conclusions that should be based on strictly quantitative data from experimental observations that justify only qualitative deductions.

Oxygen Lack.—On this point there is less difference of opinion than on any other aspect of chemoreceptor activity, for it is now agreed almost universally that the hyperpnea (and hypertension) of anoxemia, no matter how produced, result from chemoreceptor reflexes and not from a direct effect upon the central neurons. One of the interesting and unanticipated consequences of this finding has been a new viewpoint on the therapy of mental disorders, especially schizophrenia, for, thanks to the discovery that in the absence of chemoreceptor reflexes anoxemia is purely depressant to respiration (and circulation), it is now believed that depression of cortical cells elicited by drastic interference with their metabolic processes (as by shock doses of insulin, convulsant doses of metrazol, repeated inhalations of nitrogen or injections of cyanide) may reduce to normal the exalted grade of neuronal activity which presumably was responsible for the disorder and thus produce a remission or even a cure. Since the ability of anoxia to depress the central neurons is unquestioned, it follows that the total respiratory response to anoxemia is the resultant of two opposing forces—a stimulant effect by the chemoreceptor reflexes, and a depression of the central neurons by anoxia. Whether there is any important direct stimulant effect by anoxia upon the center is not quite certain, though the burden of evidence seems to the writer to be against it;[140] Gesell,[62] who has been one of the chief advocates of central stimulation by anoxia, in his most recent expression of opinion of this subject admits that such an effect is either entirely absent or decidedly diminished under the influence of anesthesia, at least. We have already seen (page 566) that the central depression produced by anoxia may be responsible at least in part for the relative smallness of the anoxemic hyperpnea. The wide individual variations in the vigor of the response to anoxemia (page 566) could be attributed to variations in the resistance of the central neurons to the depressant effects, in the extent to which the centers are stimulated directly by anoxia, or in the intensity of the stimulant discharge from the chemoreceptors. There is at present no evidence on which to decide these questions but it seems to the writer that the physician will do well to forget about the possibility that anoxia can stimulate nerve cells and to regard it as essentially depressant to them. If there is any error in this view it will be on the safe side (see page 667).

When it comes to deciding whether chemoreceptor reflexes aroused by anoxia are a factor in maintaining respiratory activity under ordinary conditions, the evidence that this is not the case is overwhelming. The fact that the breathing of normal man is not depressed when he inhales air enriched with oxygen (page 566) shows clearly that the oxygen tension of his arterial blood under ordinary conditions (about 90 mm. Hg—see Chap. XLII) is not low enough to set up a measurable chemoreceptor reflex drive to respiration. Since the hyperpnea of anoxemia is generally conceded to be a chemoreceptor response, the order of magnitude of *the sensitivity of man's chemoreceptors to reduction in arterial oxygen tension is shown simply and decisively by determining the smallest degree of such reduction at which respiration is stimulated. This corresponds with a diminution of arterial oxygen tension from 90 mm. to 67 mm. Assuming 18 per cent oxygen in the inspired air to be the threshold for anoxemic hyperpnea, the corresponding figures for oxygen saturation of the arterial blood are about 95 per cent at 90 mm. tension, about 92 per cent at 67 mm.* (Fig. 249, page 566, the curve at 40 mm. CO_2 tension.) This is the greatest sensitivity to anoxemia that we have any right to expect in the chemoreceptors of man, and it is obvious that an effective anoxic stimulus is not going to be encountered as long as the oxygenation of the blood in the lungs is at all normal.* Once the threshold of this reflex system to anoxemia has been passed,

*This conclusion contradicts that derived by Euler, Liljestrand, and Zotterman[53] from recent experiments (on cats anesthetized with chloralose) in which they found signs of chemoreceptor activity as soon as the arterial oxygen saturation fell below 96 per cent. Gesell, Lapides, and Levin[62] also report observations indicating that chemoreceptor activity (in a vagotomized dog anesthetized with morphine and chloralose) was increased when the animal was made to breathe air containing practically a normal porportion (19.7 per cent) instead of a higher one (40 per cent) of oxygen. The reader must use his own judgment in evaluating the relative importance of these results as against the numerous observations on man to which allusion has just been made. Perhaps species differences are involved; perhaps the narcotic (chloralose) was responsible for the difference—a possibility which, in view of existing information about this drug (see page 581), deserves serious consideration. It may also be that, in the experiments of Euler *et al.*, the criterion of chemoreceptor activity (action potentials in the sinus nerve) was not as trustworthy as it was assumed to be (see Schmidt and Comroe[140] p. 143).

however, further decreases in oxygen tension lead to hyperpnea of progressively increasing intensity and with regard to *effectiveness,* this is the strongest chemoreceptor stimulant of any of the three chemical changes noted above, over the range that might be encountered in the arterial blood under conditions compatible with life. The *resistance* of these structures to adverse changes in their environment (which, as we shall see, is perhaps their most important physiological characteristic) is well shown by the fact that perfusion of the carotid bodies with fluid as nearly free of oxygen as it could be made causes only an intense hyperpnea that lasts as long as the perfusion is continued and leaves the receptors apparently undamaged (Fig. 236). The central neurons are depressed or paralyzed by relatively slight anoxia (Chap. XLV).

Hydrogen Ion Concentration.—We have already seen (page 561) that, according to recent evidence, the neurons of the center are much less sensitive and the chemoreceptors considerably more sensitive to this stimulus than had previously been supposed. It is

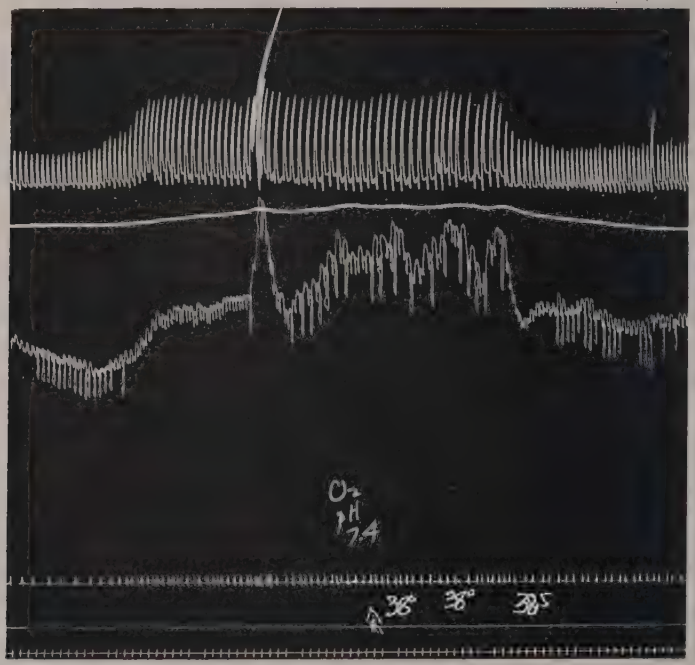


Fig. 236.—Absence of depression of chemoreceptors on perfusion with completely anoxic fluid. Upper record, respiratory movements; lower record, arterial pressure.

Perfusion of both carotid bodies of a vagotomized dog with Locke's fluid, freed of oxygen by bubbling nitrogen through it and buffered to pH 7.4 by bicarbonate equilibrated against a CO_2-N_2 mixture, instead of a similar fluid saturated with oxygen. Reflex hyperpnea and hypertension were undiminished after 4 minutes of this perfusion; on return to the oxygenated fluid, reflex effects promptly subsided. These effects could be elicited repeatedly without loss of reactivity. Nerve cells elsewhere would be inactivated by a briefer exposure to anoxia as nearly complete as this.

impossible at present to make any definite statement about the sensitivity of the center to the hydrogen ion. *The sensitivity of the chemoreceptors* has so far been investigated systematically only by one group (Fig. 237), who found that the smallest change in acidity that sufficed to elicit definite (though slight) reflex changes in respiration (in lightly anesthetized, vagotomized dogs whose carotid bodies were perfused with buffered saline solutions) corresponded with a shift of pH 0.1 in either direction. This is a relatively large shift to be associated with a minimal respiratory effect; inhalation of carbon dioxide

or muscular exercise would produce much greater hyperpneas with much smaller shifts in pH, indicating either that the chemoreceptors of man are much more sensitive than those of the dog or that chemoreceptor responses to changes in arterial pH per se are not likely to be a factor in respiratory control under any but very unusual conditions. The latter alternative appeals to the writer as the more probable, but this is a matter of opinion. In the animal experiments just alluded to larger increases in acidity produced more intense reflex hyperpneas and with shifts of the order of pH 0.5 or more, responses approaching those elicited by anoxemia or cyanide could be elicited consistently. Thus it is possible by existing evidence to account for the dyspnea of severe acidosis in man by strong stimulation of his chemoreceptors by means of the hydrogen ions themselves, and it is also possible that the central neurons are not directly stimulated by the hydrogen ion, but the reader should clearly understand that the latter remains to be proved. The resistance of the chemoreceptors to adverse circumstances was strikingly exhibited in the same experiments, for perfusion of the carotid bodies of dogs with Ringer's fluid as acid as pH 6.0 elicited only a strong reflex hyperpnea and apparently did not damage the reflex system.

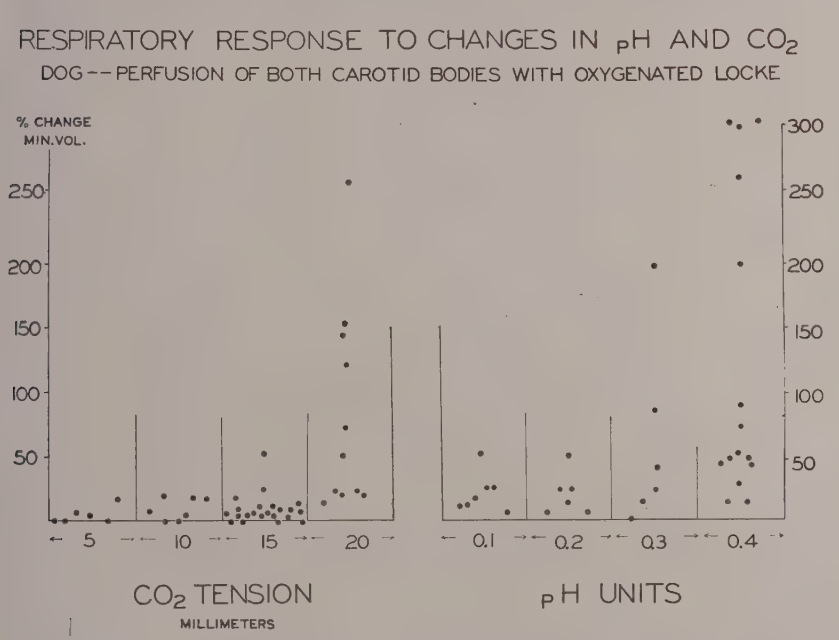


Fig. 237.—Each dot indicates one observation (on a vagotomized dog under light anesthesia by chloralose) when perfusion fluid was altered as indicated (i.e., when CO_2 tension was raised 5, 10, 15, or 20 mm. Hg, or when acidity was increased to the extent of a decrease of pH 0.1, 0.2, 0.3, or 0.4). Observations were made on 12 dogs all of which showed very strong reflex responses to perfusion with anoxic fluid. (From Proc. Soc. Exper. Biol. and Med. 42: 31, 1939.)

Carbon Dioxide.—It is on this point that the greatest difference of opinion exists; this (in the writer's opinion) is because carbon dioxide unquestionably owes an important part of its effects to an action directly on the central neurons and the disagreements have to do with the proportion of the effect due to this factor as compared with that attributable to the reflex component. There is no possibility here of ascribing an exclusive or even preponderant rôle to the chemoreceptors. On the other hand, all who have made pertinent observations agree that carbon dioxide can stimulate the chemoreceptors. Decision about the relative parts played by the reflexes and by direct effects on the central neurons in the respiratory response of an intact animal or man to changes in the carbon dioxide ten-

sion of the arterial blood must therefore rest entirely upon truly quantitative comparisons of sensitivity, power, speed and resistance.

As for *sensitivity*, in the only systematic investigation of this point now available (Fig. 237), the threshold (i.e, the smallest change in CO_2 tension in the fluid perfusing the carotid bodies to which there was a definite though slight respiratory response) of the chemoreceptors of lightly anesthetized, vagotomized dogs was found to be about 10 mm., while the corresponding threshold of the central neurons (i.e., the increase in arterial CO_2 tension at which hyperpnea began in the absence of chemoreflex activity) was in the vicinity of 3 mm.[143] These are the smallest changes in carbon dioxide tension to which the two systems have as yet been shown to respond in one species of animal (the dog) under comparable experimental conditions; whether they are applicable to other animals (including man) and other conditions is perhaps debatable, but these are the only figures now available for comparing the sensitivity of the two systems. Obviously they indicate the central neurons to be much the more sensitive.

The *speed* with which the chemoreceptors react to carbon dioxide was claimed[79] to be greater than that of the central neurons, but the only direct investigation of this point with methods capable of yielding the data required to settle it had an entirely negative outcome.[143] If (as all existing evidence indicates) the central neurons are more sensitive than the chemoreceptors to a rising carbon dioxide tension in the blood, any hyperpnea so produced in an intact animal would necessarily begin as a purely central response. Although it is possible to devise an experiment in which, by injection of solutions having a very high tension of CO_2 directly into the carotid, an instantaneous reflex hyperpnea can be elicited, this shows only that the chemoreceptors can be stimulated by carbon dioxide if the tension is high enough (which has not been denied); it does not warrant any deductions with respect to physiological importance.

The relative *power* of the central and reflex components of the response to carbon dioxide is shown very strikingly by an experimental observation that has often been made and never refuted, i.e., that the total increase in pulmonary ventilation produced by inhalation of carbon dioxide is just as great when chemoreceptor reflexes are inactive as when they are active (Fig. 233[125]). The situation here is obviously quite unlike that existing in anoxemia (Fig. 233), the hyperpnea of which is totally lacking in the absence of the reflexes. Although the CO_2 experiment does not necessarily prove that there is no reflex component at all in the response of the intact animal to this gas, it shows conclusively that the direct effect of CO_2 on the central neurons can be so strong that the reflex component can be withdrawn without its absence being noted.* Actual comparisons of the relative strengths of the reflex hyperpneas produced by carbon dioxide and other stimuli are few, but they are consistent in showing CO_2 to be much weaker than anoxemia in this respect.[140] This does not mean that chemoreceptor reflexes cannot be aroused by carbon dioxide, for all who have investigated the point agree that they can be. Under normal conditions the reflex component probably is unimportant, because the central neurons respond sooner and much more powerfully than the chemoreceptors and the latter come into play only when the central response cannot prevent a rise in arterial carbon dioxide tension sufficient to affect the relatively insensitive chemoreceptors. Under abnormal conditions in which the sensitivity of the central neurons to carbon dioxide is reduced, the chemoreceptor factor becomes much more important, as we shall see (page 594).

The *ruggedness* of the chemoreceptors (i.e., their ability to continue to function in the face of adverse conditions) is manifested again here: according to all who have made actual observations bearing on the point, these structures are not depressed but are only stimulated progressively by any increase in carbon dioxide tension to which they have so far been exposed. The fact that the respiratory response to rising carbon dioxide percentages in the inspired air does not increase steadily but reaches a maximum at a relatively low figure (9 per cent) and then declines (see page 565), must be attributed to the narcotic action of CO_2 upon the central neurons, not to decreased activity on the part of the chemoreceptors.

*This conclusion is supported by the experimental observations recently reported by Gesell, Lapides, and Levin,[62] who found that inactivation of the chemoreceptors during inhalation of a rather strong (6.5 per cent) mixture of CO_2 in oxygen had no measurable effect on respiration whereas similar inactivation produced distinct depression of breathing in the same animal when the CO_2 content of the inspired mixture was lower and the hyperpnea apparently was less intense.

Other Stimuli.—When the fluid perfusing the carotid bodies of anesthetized dogs is suddenly cooled, in a certain proportion of cases respiratory depression occurs, and when the fluid is again warmed hyperpnea sets in (Fig. 238); the effect can be proved to be reflex because it is abolished by inactivation of the sinus nerves. The most obvious explanation is that cooling inactivates the reflex system, but the situation is not so simple as this, as the following observations show: first, if cyanide is added to the perfusing fluid when the respiratory depression is at its height a reflex hyperpnea ensues—weaker perhaps than that elicited by the same dose at normal temperatures but none the less a real response; second, cooling of the perfusing medium may still cause depression of breathing and warming a hyperpnea, even though the fluid is a buffered saline mixture saturated with oxygen (tension more than 150 mm.), alkaline (pH 7.5), practically free of carbon dioxide (tension less than 1 mm.), and entirely free of any mysterious humoral material—in brief, when there is nothing to account for chemoreceptor activity that could be removed by cooling the fluid and thus cause respiratory depression. For these reasons it is permissible to suspect that the receptors responsible for these effects under such circumstances may not be activated by chemical factors in the blood but may be responding directly to the changes in temperature. Because the respiratory effects of even extreme changes in temperature are relatively slight at best, it is obvious that the number of temperature-sensitive receptors in the carotid bodies must be rather small, if indeed there are any at all.

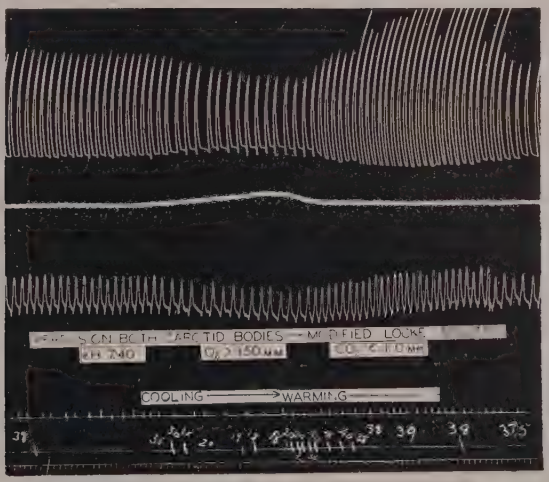


Fig. 238.—Effects of cooling and warming on chemoreceptors.
Perfusion of both carotid bodies (of a vagotomized dog lightly anesthetized with morphine and chloralose) with Locke's solution of pH 7.40, saturated with oxygen (tension above 150 mm. Hg) and free of CO_2 (tension less than 1 mm.). Note depression of breathing (minute volume shown in upper signal line, each stroke indicating 500 ml.) on cooling perfusing fluid from 38° to 18° C. and subsequent stimulation on warming fluid back to 38°. In other similar tests NaCN, injected into perfusing fluid when depression was at its greatest (temperature at its lowest) elicited a marked reflex hyperpnea.

The hyperpnea produced by a number of *drugs and poisons* (cyanide, sulfide, nicotine, lobeline, etc.), like that of anoxemia, is generally conceded to be due to chemoreceptor reflexes. Any direct effect that these substances exert on the central neurons appears to be purely depressant. The same statement can also be made about vasomotor stimulant effects from these drugs with the reservation that nicotine, lobeline, and other compounds that are capable of stimulating autonomic ganglia, can do this just as well without the chemoreceptors as with them; larger doses are, however, required than those that suffice to produce strong chemoreceptor stimulation, and the latter therefore accounts for the first effects (on circulation as well as respiration) of a rising concentration of any of these

substances in the blood. Very high concentrations of any effective stimulant to the chemoreceptors can also produce (through the carotid body of the dog) reflex stimulation of the cardioinhibitory center and thus prevent, or actually reverse, the rise in blood pressure that would otherwise result from the concomitant stimulation of the vasomotor center. This has no practical importance, for the requisite concentrations can be attained only by intravascular injections of large doses; its chief importance lies in its being an avoidable source of disagreement among different investigators of the influence of chemoreceptor reflexes upon the circulation.[39]

The list of chemicals that have been reported to be capable of stimulating the chemoreceptors is quite long, but it is probably significant that a considerable number of them can be gathered into two groups: first, those that would produce anoxia in the receptors either by interfering with the intracellular enzyme system (cyanides, sulfides) or by increasing the oxygen utilization (dinitrophenol, dinitrocresol); second those that have "nicotinic" properties (i.e., a stimulant, followed, in larger amounts, by a depressant action on autonomic ganglia, this group including nicotine, coniine, lobeline, hordenine, sparteine, and choline and its esters such as acetyl choline). A number of others, however, do not fall into either category (see Schmidt and Comroe[140] for a list of them), one of the outstanding instances being potassium salts. The latter have been found to depress the chemoreceptors (as well as the extremely resistant pressoreceptors) when the stimulant dose is exceeded or is frequently repeated, which makes it probable that this is a toxic action rather than an expression of a physiological rôle of potassium in the regulation of chemoreceptor activity. The latter conclusion probably applies also to acetyl choline, for the doses required to elicit chemoreceptor responses are relatively enormous.[140]

The Physiological Stimulus to the Chemoreceptors.—In the writer's opinion, existing information on this point warrants no conclusion more specific than that *these structures are so organized that they give rise to afferent impulses when their chemical equilibria are sufficiently disturbed, that suitable disturbances can probably be brought about in a number of different ways, and that among the agents capable of doing this are the three common chemical effects of metabolic activities, i.e., decreased oxygen tension, increased hydrion concentration, and increased carbon dioxide tension.* There may be some receptors here that respond to temperature changes *per se* and are not really chemoreceptors, but these are probably scanty and unimportant if present at all. There is at present no reason to believe that all chemoreceptor phenomena can be attributed to a common chemical change within them or that a specific chemical mediator is concerned in their activity. The only chemical stimulus to which both the chemoreceptors and the central neurons are known to respond actively is carbon dioxide and to this the center is much more sensitive than the chemoreceptors; carbon dioxide is also a relatively weak stimulus to the receptors. Oxygen-lack is the strongest physiological stimulus to these structures over the range compatible with life. Increased hydrion concentration can rival anoxemia as a stimulus but the changes necessary for maximal chemoreceptor activation are greater than pH 0.5 and are therefore not likely to be encountered in an intact animal or man.

Summary.—The part played by chemoreceptor reflexes in adjusting pulmonary ventilation to the requirements of the body must be negligible under normal conditions. This is indicated by the undoubted facts that the hyperpnea of exercise is not associated with any change in the blood that could stimulate these structures (page 604); that the hyperpnea of carbon dioxide inhalation has not been found to be modified in any measurable way by removing the chemoreceptor influence (page 590); and that oxygen inhalation does not depress the breathing of normal man (page 566). It has been claimed by some workers in this field that the chemoreceptors are continually stimulated by the carbon dioxide tension normally present in the arterial blood and that the reflex drive thus induced is a factor of importance in maintaining the activity of respiration even under resting conditions. Although this is undoubtedly true when the central neurons are severely depressed (see below) there is no valid evidence to indicate a similar relation when they are still highly reactive

to carbon dioxide; under the latter circumstances inactivation of the chemoreceptors often does not depress breathing at all, and when it does, the depression is slight and momentary.[143] In the writer's opinion, *the place of these reflexes in the body's economy lies, not in their sensitivity to the factors which (acting directly on the central neurons) normally regulate breathing, but in their ability to withstand, and to respond under, adverse circumstances which seriously interfere with the functional capacity of the central neurons. By virtue of this ruggedness the chemoreceptors are enabled to set up a powerful reflex drive and thus to maintain the activity of the neurons when the latter have lost their ability to respond to their normal stimuli.* It is not unlikely that other nerve tissues would be stimulated progressively as the chemoreceptors are when exposed to increasing anoxemia, acidosis and hypercapnia, if it were not for the fact that an excess of any of these stimuli decreases the ability of these more delicately organized tissues to function.

Table XIX summarizes existing information with regard to the threshold of the respiratory center and the chemoreceptors to decreased oxygen, increased carbon dioxide, and increased acidity. The figures are in each case the smallest that can be supported by actual experimental evidence. It is at once evident that the sensitivities of the two structures to these stimuli are utterly different. There is some reason to question the value of the CO_2 comparisons for here the sensitivity of the respiratory center of normal, unanesthetized man must be directly compared with that of the carotid bodies of dogs as determined by saline perfusions of the structures in anesthetized, vagotomized animals subjected of necessity to rather extensive operative procedures. It is wholly probable that the sensitivity of the chemoreceptors of man to carbon dioxide (and to the hydrogen ion) is greater than these figures indicate, but this is as yet undetermined; it is also (by existing methods) undeterminable. If we can judge from the threshold to anoxemia, the chemoreceptor thresholds ascertained in these animal experiments are not very different from those of intact normal man,[140] which indicates again the ruggedness of the reflex system. In any case, these are the only data now available for comparison. The size of the gap between the sensitivity of the chemoreceptors and that of the center is indicated more clearly when we compare these thresholds with data obtained from a normal man by analyses of blood collected by direct arterial and venous puncture (Table XX). If, when the subject was at rest, arterial blood were suddenly to be completely replaced by venous, the change would still be well below any known chemoreceptor threshold except for the diminution in oxygen tension. Even when the subject was exercising (on a stationary bicycle) and his pulmonary ventilation had increased seven-fold (which was the extent of the increase in oxygen consumption) the increase in carbon dioxide tension that would result from replacement of arterial by venous blood would be of an order that elicits only a weak stimulation of the carotid chemoreceptors in animal experiments and the increase in hydrion concentration would still be below any demonstrated chemoreceptor threshold.

TABLE XIX

SMALLEST CHANGE IN ARTERIAL BLOOD BY WHICH HYPERPNEA HAS BEEN PRODUCED

STIMULUS	KNOWN THRESHOLD OF RESP. CENTER OF MAN	KNOWN THRESHOLD OF CHEMORECEPTORS
Decreased O_2 tension	More than 23 mm. Hg*	23 mm. Hg (man-Ellis[52])
Increased CO_2 tension	0.075 mm. Hg*	10 mm. Hg (dog[142])
Decreased pH	?*	−0.1 (dog[142])

*These values are derived as follows:—The hyperpnea of anoxemia is assumed to begin as a reflex phenomenon in man as it has been shown to do in animals; the threshold of the respiratory center to anoxemia is therefore listed simply as being higher than that of the chemoreceptors. The threshold of the human respiratory center to carbon dioxide is calculated from the statement by Haldane[67] (page 185) that one-twentieth of the 1.5 mm. change that doubles pulmonary ventilation would affect breathing measurably. For reasons that have already been given (page 567), it is impossible at present to assign any definite value to the sensitivity of the respiratory center to the hydrogen ion.

TABLE XX

COMPOSITION OF ARTERIAL AND VENOUS BLOOD OF A NORMAL MAN AT REST AND DURING EXERCISE SEVERE ENOUGH TO INCREASE OXYGEN CONSUMPTION SEVEN-FOLD*

	AT REST (OXYGEN CONSUMPTION 250 ML. PER MINUTE)			EXERCISE (OXYGEN CONSUMPTION 1750 ML. PER MINUTE)		
	ARTERY	VEIN	A-V DIFFERENCE	ARTERY	VEIN	A-V DIFFERENCE
O_2 tension—mm.	78	40	38	75	31 ..	44
CO_2 tension—mm.	40	45.4	5.4	38	54.8	16.8
pH (serum)	7.425	7.399	0.026	7.351	7.278	0.073

*From J. Biol. Chem. 73: 749, 1927.

Chemoreceptor Reflexes Under Abnormal Conditions

Under deep narcosis the situation described above may change greatly, but the result varies with different narcotics. Marshall and Rosenfeld[111] were the first to point this out; they found that phenobarbital and morphine brought about in dogs and cats a situation in which oxygen inhalation caused depression or failure of breathing while other drugs (chlorbutanol, urethane, paraldehyde and alcohol) did not. In animals given phenobarbital and morphine addition of carbon dioxide to the inspired oxygen did not prevent the occurrence of respiratory depression when oxygen was inhaled but after denervation of the carotids and aorta oxygen inhalation no longer caused depression of breathing. They concluded that under the influence of these drugs breathing is maintained—"almost if not entirely by the anoxemic stimulus acting through the sino-aortic mechanism." Their observations have been confirmed and the above interpretation is now generally accepted. It is interesting that ether appears to produce relatively greater depression of the response of the reflex system to anoxia than of that of the center to carbon dioxide while chloralose is perhaps most likely of all narcotics to swing the balance to the opposite extreme[139]—a point of importance in connection with the widespread use of chloralose in experiments intended to elucidate the physiology of chemoreceptor reflexes (see page 581).* The results obtained by stimulation or inactivation of the chemoreceptors thus appear to depend greatly upon the type of anesthesia as well as its depth, and it is probable that there are also species differences.

The reasons for these peculiar effects are still uncertain, but they become understandable if we recall that an excess of carbon dioxide is depressant to living cells in general and the cells of the respiratory center are exceptional only in that they happen to have the highly specialized property of being strongly stimulated by very small increases in the tension of this gas when they are normally reactive. When the cells are disorganized by narcosis, or anoxia, or both, they lose this specialized faculty more or less completely and then the depressant effect that is common to all living cells is the dominant or sole result of further increase in carbon dioxide tension. As we have seen (page 564) a great increase in carbon dioxide tension may depress the center even when it is normal. The chemoreceptors, however, appear to be made of sterner stuff: as far as existing information goes they are not appreciably depressed by any increase in carbon dioxide tension, but are only stimulated progressively as the stimulus is increased. The same is also true of their response to increased acidity and to decreased oxygen tension; both of these—particularly the latter—when carried beyond certain very narrow limits depress the activities of living tissues in general, but the chemoreceptors have not yet been shown to respond with anything but stimulation even to changes in these stimuli that would produce immediate failure of the center if they were elicited there (see page 592). Perhaps it is because the chemoreceptors can still set up a powerful drive to the respiratory center after the central neurons have ceased re-

*Gesell, Lapides, and Levin[62] have recently attributed to carbon dioxide an action essentially similar to that of ether, i.e., a progressive diminution of the effectiveness of the reflex influence as the tension of CO_2 in the blood increases. They reach this conclusion from the observation that (in a vagotomized dog narcotized with morphine and chloralose) inactivation of the chemoreceptors (by cooling of the nerves) caused less and less respiratory depression as the carbon dioxide content of the inspired air increased until finally no depression at all occurred at a CO_2 content of 6.5 per cent. Although an ether-like action by relatively high tensions of carbon dioxide is not unlikely in view of the well-known narcotic properties of this gas, it is possible to explain these observations on the very different basis (see page 590) that the central neurons were simply being stimulated maximally at the higher percentage of carbon dioxide.

sponding to anything else that a series of respiratory efforts are commonly seen a minute or so after the pulse has become imperceptible; these terminal efforts may be due to access of venous blood to the chemoreceptors. This indicates not only that the chemoreceptors can tolerate conditions that are rapidly fatal to the centers, but also that afferent impulses from the chemoreceptors can drive the cells of the center after the latter have ceased entirely to respond to changes in their immediate environment. To characterize this property the writer suggested a term which the older cardiac physiologists have applied to the Purkinje system in the heart (see Rothberger[136]), i.e., the *ultimum moriens,* as descriptive of the place of the chemoreceptors in the respiratory regulating system, meaning that it is the part of the system which is last to surrender its functions in the face of adverse circumstances.

SCHEMA SHOWING ROLES OF AORTIC AND CAROTID BODIES IN RESPIRATORY AND CIRCULATORY RESPONSE OF THE DOG TO ANOXIA

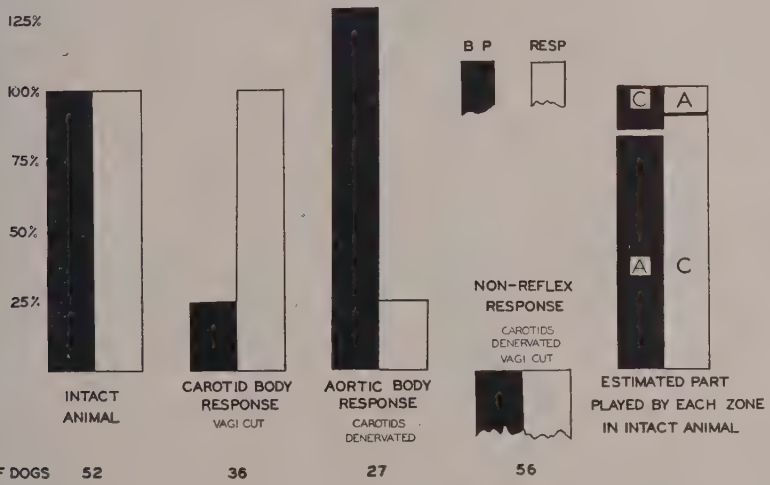


Fig. 239.—Schema showing rôles of aortic and carotid bodies in respiratory and circulatory response of the dog to anoxia. If the increase in respiration and blood pressure (B.P.) due to anoxia is regarded as 100 per cent for the intact dog, the *carotid* bodies alone are usually capable of producing *respiratory* stimulation equal to that of the entire dog (100 per cent), while the *aortic* area alone usually produces a rise *in B.P.* even greater than that in the intact animal (due to removal of carotid body reflex bradycardia and carotid sinus inhibition by complete carotid denervation). The last column is an estimate of the part played by carotid reflexes (C) and aortic reflexes (A) when both are functioning simultaneously. (From Comroe: Am. J. Physiol, 127: 176, 1939.)

Thus we can envisage the part played by these reflexes in respiratory control as that of furnishing a reflex drive to the center when the latter unaided is unable to prevent relatively marked and potentially dangerous changes in the chemical composition of the arterial blood. The conditions under which this is most likely to occur are: (1) anoxemia, no matter how produced; (2) addition of relatively high concentrations of carbon dioxide to the inspired air; (3) derangement of the reactivity of the center to changes in its environment, as by anoxia, trauma, disease, or particularly by narcotic drugs; (4) poisoning by metabolic acids (uncompensated acidosis) or by the drugs and poisons listed above as stimulants to the chemoreceptors, for all of these are likely to depress or paralyze the center apart from reflex stimulation.

Differences in the Total Chemoreceptor Activities of the Carotid and Aortic Regions.—So far we have made no effort to distinguish between the chemoreceptor reflexes from the two regions. As indicated above (page 576) they are qualitatively identical with one exception, which is the reflex cardiac inhibition that is aroused by strong stimulation of the carotid chemoreceptors of the dog; no comparable result is known to occur in that animal from stimulation of the aortic chemoreceptors; this reflex bradycardia is probably an experimental curiosity, elicited only by intravascular injections of large doses of certain drugs and therefore devoid of practical importance. There are wide individual variations in the partition of the remainder of the anoxic chemoreceptor response (hyperpnea and hypertension) between the two zones, but in a long series of observations on dogs Comroe[39] found an unmistakable tendency for the carotid reflexes to account for most of the hyperpnea, the aortic reflexes for most of the hypertension (Fig. 239). Some of the hypertension undoubtedly arises from stimulation of the carotid bodies and in the occasional dog vasomotor reflexes from these structures are quite marked, but in the average intact animal it seems clear that by far the largest part of the total hypertension produced by anoxemia is due to reflexes from the aortic chemoreceptors. In cats Comroe found the individual variations to be even wider than in dogs, but there was a definite tendency for the carotid chemoreceptors to account for more of the total hypertension and for the aortic structures to be responsible for a larger share of the total hyperpnea than was the case in the dog. In view of these species variations it is impossible to state anything definite about the probabilities in man.

The Significance of Respiratory Reflexes From the Carotids and Aorta.—The fact that respiration can be influenced profoundly by reflexes aroused in pressoreceptors and chemoreceptors that lie in no relation whatever with the ventilating surfaces but are actually (or practically) imbedded in the walls of major arteries is of itself remarkable. The inhibitory effect on respiration of increased activity of the pressoreceptors may be classed as a laboratory curiosity devoid of practical importance, but that cannot be said of the reflex hyperpnea (and hypertension) aroused by increased chemoreceptor activity, for, as noted above, such reflexes constitute an important factor in the body's defense against emergencies such as anoxemia, dangerously high concentrations of carbon dioxide in the inspired air, marked reduction in the sensitivity of the respiratory center to chemical stimuli, and poisoning by foreign chemicals and by products of the body's own metabolism. As far as anoxemia is concerned, chemoreceptor activity can fairly be regarded as the most important single item in the body's defense (see Chap. XLV) and it is not unlikely that many persons are alive today only because this activity was retained when narcotic drugs were given in large dosage. This is all the more remarkable when we consider that such reflexes do not play any comparable part (or indeed any demonstrable part at all) in the adjustment of pulmonary ventilation to changes in metabolic activity under ordinary circumstances such as muscular exercise (see page 593); they could be involved only when the exertion is so extreme that the blood becomes definitely more acid. Now it is unlikely that a reflex system such as this would be present so uniformly in animals whose ancestors were probably never exposed to anoxemia or poisoning by foreign chemicals and many of whom were never called upon for the extreme effort required to elicit an acid shift in the blood, if the system were not related to an organization that was of fundamental importance in some remote ancestral form and has been relegated to

a subordinate position by the development of the more sensitive and more highly specialized structures in the mammalian central nervous system. We have already seen that such a suggestion was first recorded by Marshall and Rosenfeld[111] who found that cats or dogs, when deeply poisoned by certain narcotics, are likely to cease breathing for long periods (sometimes permanently) if they are made to inhale oxygen, with or without carbon dioxide; since the phenomenon did not occur after denervation of the carotids and aorta, they concluded that breathing must have been maintained by reflexes aroused in those areas by anoxemia. They cite the experiments of Babák[9] who found that the respiratory movements of tadpoles are greatly influenced by changes in the oxygen tension of the environmental water but are affected little or not at all by changes in the carbon dioxide tension—a relationship very different from that existing in the mammalian respiratory center but very similar to that in the chemoreceptors. They suggested—"that when the mammalian organism is threatened with dissolution from respiratory failure it may adapt itself under certain conditions by reverting to a primitive type of respiratory control which seems to be normal for some of the lower vertebrates."

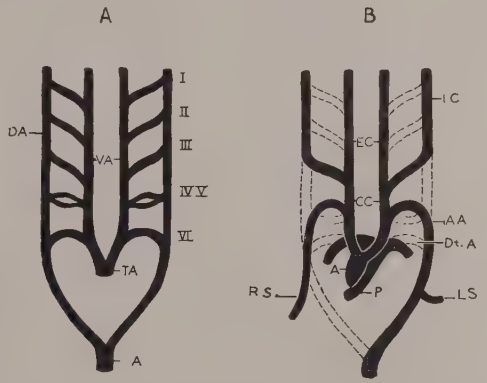


Fig. 240.—Diagram showing development of carotid sinuses and aortic arch from branchial arteries of embryo.

A, arrangement in embryo: primitive dorsal (*DA*) and ventral (*VA*) aortae and branchial arches (*I* to *VI*); *TA*, truncus arteriosus; *A*, unpaired dorsal aorta.

B, arrangement in adult: *IC*, internal carotid; *EC*, external carotid; *CC*, common carotid; *AA*, aortic arch; *DtA*, ductus arteriosus; *LS* and *RS*, subclavian arteries; *A*, aorta; *P*, pulmonary artery.

This suggestion, based on phylogenetic considerations, is rendered considerably more plausible as well as more attractive when ontogenetic factors are also taken into account. The carotid and aortic reflex systems in mammals are derived from the branchial arch system of the embryo and therefore they are related to a primitive organization for water-breathing (the gills). In the mammalian embryo the truncus arteriosus, arising from the aorta, divides into two ventral trunks in the neck and from each of these six branchial arch vessels arise, run dorsally and headward, and unite in two dorsal trunks which run back to the aorta (Fig. 240). As development proceeds the first and second branchial arch vessels of each side disappear; the ventral trunk in this vicinity gives rise to the external carotid, the dorsal trunk to the internal carotid. The third arch vessel on each side becomes the communication between the external and internal carotid, which corresponds with the carotid sinus in the adult. The fourth arch vessel on the left side becomes the aortic arch, while its mate becomes the right subclavian artery. The fifth pair fuse with the fourth at an early stage. The sixth give rise to the pulmonary artery.

The development of reflex systems in relation with the carotids and aorta appears to be connected with the early appearance of ectodermal nerve elements in proximity with the mesodermal cells from which the arterial walls are subsequently developed. In the third arch, elements from the glossopharyngeal nerve come into relation with mesoderm at an early stage (Boyd[29]) and it is probable that the chemoreceptors of the carotid body arise from the changes thus imposed on the two sets of cells; it is suggestive that muscle can be shown to be lacking in the occipital artery of the adult dog in the region of the carotid body but to be present just beyond the latter (Addison[1]), as though mesodermal material that should have formed muscle was diverted by the ectoderm of the developing glossopharyngeal nerve to form chemoreceptors. The aortic body (or bodies) probably have a similar origin from the mesoderm of the fourth arch and the ectoderm of the vagus nerves (Boyd). As for the pressoreceptors, their presence in the same regions as the chemoreceptors suggests a similar origin, and the lack of muscle coat in the carotid sinuses (Addison) may mean that here mesoderm had combined with embryonic neural elements to form pressoreceptors. If a lack of muscle in the coat of a major artery is always to be explained in this manner one would be entitled to suspect the presence of some special reflex system wherever such a lack exists, but why the fusion of mesodermal and ectodermal elements should form chemoreceptors in one case, pressoreceptors in another, remains unexplained, and it is unlikely (for reasons to be given immediately below) that receptors elsewhere would have functional significance similar to either of these.

For our present purpose the important point is that the chemoreflex and pressoreflex systems of the carotids and aorta can be related to the survival (in a relatively unaltered state) in the air-breathing terrestrial mammal of a system which would have had much more obvious significance in a water-breathing vertebrate. In the latter the branchial arteries persist, the peculiar capillary system characteristic of the gills is developed, and the whole structure is moved by muscles whose contraction is presided over and synchronized by the respiratory center in accordance with the requirements of the organism for a respiratory gas exchange. In such an animal a chemoreflex system capable of informing the respiratory center about changes in the aquatic environment would have obvious advantages. Furthermore, if some such system did exist it would be to the organism's advantage to have it regulated by changes in the tension of oxygen rather than carbon dioxide, for the latter is so soluble in water at ordinary temperatures that an increase in the tension of the gas would be unlikely to occur in water, as the result of stagnation or pollution, until the oxygen tension had been dangerously reduced. And since the main purpose of such a system would be to permit the organism to survive or escape from a noxious environment the reflexes should be both very resistant to depression by marked changes in the environmental fluid and capable of producing and maintaining a drive to the respiratory mechanism under circumstances to which the more highly differentiated nerve cells of the center would succumb if left to their own devices.

These are precisely the functional attributes which distinguish the chemoreceptors from the cells of the respiratory center of the air-breathing animal. In the development of such an animal the branchial arterial system never acquires a respiratory function and much of it becomes altered almost beyond recognition. It is probably significant, however, that the regions in which specialized reflexes appear and remain are also those in which the changes during development are least (Fig. 240); this suggests that the reflexes represent structures that are relatively primitive and undifferentiated. If we assume that the chemoreceptors subserve in the air-breathing animal the functions that they presumably would have subserved in the aquatic organism, granting that the environment of the receptors has become arterial blood instead of environmental water, we can account for most of their anatomical and physiological peculiarities. As for the pressoreceptors, there is as yet no evidence that corresponding structures in aquatic animals can give rise to reflex changes in the respiratory movements, but it is known[108] that in some such animals (the dogfish *Squalus acanthias* and the amphibian mud-puppy *Necturus maculosus*) the gills contain pressoreceptors that are capable of altering the heart rate reflexly. If this part of the carotid sinus pressure reflex can be aroused by changes in pressure in the gill arteries it is certainly not improbable that the rest of it can also. According to Krogh[95] gill breathing consumes an amount of energy which, compared with that in the air-breather, is relatively enormous in proportion to the amount of oxygen absorbed, and this sets limitations to the ability of such an animal to increase his metabolic activity; the fish is enabled to compensate for this, however, because he can secure a perfectly adequate gas exchange while swimming actively, simply by keeping

his mouth open and without any respiratory movements whatever. Perhaps inhibition of breathing and relaxation of the respiratory muscles on rise in pressure in the gill arteries are part of the organization for this. In the air-breathing mammal an arrangement such as this could never be advantageous; on the contrary it could be deleterious if it were sufficiently developed to lead to inhibition of respiratory movements whenever blood pressure rose, for the increased respiratory activity required during muscular exercise would thus be more or less completely prevented. Even under resting conditions the inhibition of the vasomotor center brought about by the increased pressoreceptor activity resulting from a rise in blood pressure would be opposed by an increase in the chemical stimulus to the same center in consequence of inhibition of respiration. Thus it is fortunate that the pressure reflexes have assumed as their principal function the regulation of blood pressure and heart rate and that respiratory effects from them are demonstrable only under special circumstances in the laboratory.

Protective Reflexes.—In this category we may consider a group of coordinated, purposeful responses to the inhalation of irritant materials. A *sneeze* is elicited by irritation of the mucous membrane of the nose, a *cough* by irritation of the respiratory passages beyond the nose. The impulses responsible for a sneeze are set up by irritation of sensory receptors of the trigeminal nerves and probably also by stimulation of the olfactory end-organs, while those which lead to a cough arise in the pharyngeal distribution of the glossopharyngeal and in the sensory endings of the vagus in the larynx, trachea, and bronchi. Both reflexes are characterized by a deep inspiration and a violent expiration; in a cough the vocal cords close completely when the inspiration is completed and do not open until the expiratory movement is well under way, so that the outward movement of air is an explosive one. It is interesting to note that once the deep inspiration has been made the violent contraction of the expiratory muscles is harder to control than if the inspiration is voluntarily kept shallow. Perhaps this is another instance of the interaction of the Hering-Breuer reflex and the reciprocal innervation of the inspiratory neurons (see page 557). The unusually complete reflex inhibition of the inspiratory neurons which follows a deep inspiration may automatically cause the forced expiration because it releases the expiratory neurons from the inhibition which the inspiratory cells ordinarily exert upon them.

These responses to inhalation of irritant material are considerably modified during anesthesia and probably also when the individual is unconscious for other reasons. Irritation of the upper air passages now causes apnea in the relaxed position (passive expiration). This part of the reflex is actually present in the conscious subject, but it is overshadowed by violent expiratory efforts which may be completely absent in the unconscious state. In the rabbit the inhibitory reflex is so powerful that intense irritation of the upper air passages may if continued cause fatal asphyxia, but this could not occur in most other animals or in man. This reflex is entirely abolished by anesthesia deep enough to remove the tendon and ocular reflexes; it operates in the early stages of inhalation of irritant anesthetic vapors but not in the stage of complete anesthesia. The reflex which causes a cough in the conscious subject takes the form of active expirations in the unconscious or anesthetized individual. As a result respiration is accelerated and it may also be increased in depth. Unlike the upper respiratory reflex, this continues to be active throughout the safe range of anesthesia. When it disappears respiration becomes slow and shallow and soon ceases entirely. It is undoubtedly a large factor in the relative safety of ether as an anesthetic, for this substance is more irritant than any of the other anesthetics that are commonly given by inhalation; by reason of this fact respiration is driven by reflexes from the lower respiratory passages and the depression of the center which ether produces is effectively counteracted. Substitution of a less irritant vapor, such as chloroform, removes the reflex stimulation while retaining the central depression. Such substitution is therefore a dangerous thing when the subject is already under anesthesia by ether.

Irritation of the larynx may cause spasm of the glottis, and irritation of the lower passages may lead to spasm of the bronchial muscle. These effects are likely to follow exposure to violent irritants, such as the poison gases used in modern warfare. They may also be encountered in civilian life, for some of the mechanical refrigerators now in use contain ammonia or sulfur dioxide, and sudden escape of these agents may produce all of the phenomena just mentioned. Such effects are probably due to actual damage to nerve endings and not to stimulation of specialized sensory receptors. They do not disappear as soon as the noxious agent is removed.

Other Reflexes.—Impulses carried through the *stellate ganglia* are said by Cromer and Ivy[43] to be important in the regulation of breathing, for after removal of the ganglia strong stimulation of the central end of a vagus nerve may cause a fatal apnea in dogs. This does not occur if the stellate ganglia are intact, for breathing then escapes from the inhibition produced by vagus stimulation before death occurs. The nature of this influence and its significance in the control of respiration have not yet been made evident.

Pain causes respiratory stimulation, but this is probably only because it sets up a generalized excitation which happens to include the respiratory neurons. The same statement is equally applicable to the respiratory changes associated with emotional disturbances and with unusual visual, auditory, and tactile sensations. These effects are only complications when respiration is normal, but they may be important under special circumstances. Advantage is taken of the respiratory stimulant effect of pain in the common procedure of spanking a newborn child to make it breathe, and sensations of cold aroused by the infant's sudden change in environment doubtless also play a part in arousing the center to activity. The practice of dashing cold water on the skin and of slapping the hands or pinching the cheeks of one who has lost consciousness rests on the same basis. In all probability the beneficial effects of inhalation of ammonia ("smelling salts"), the swallowing of irritants (whisky or brandy, aromatic spirits), or of hypodermic injection of irritants (camphor, ether, alcohol) are also due to reflexes of this same type.

Prolonged and severe pain may also cause sufficient increase in breathing to lead to acapnia (deficiency of CO_2 in the blood). If now the pain is suddenly relieved, as by anesthesia, breathing may cease because the reflex influence which had been maintaining it at a high level is removed and the chemical stimulus to the center is insufficient to keep it active without the reflex. Henderson and Scarbrough[76] called attention to this as a cause of sudden death during anesthesia. The same reasoning can be applied to excitatory respiratory reflexes in general. When the respiratory center is depressed by trauma, circulatory disturbances, or drugs, it becomes less responsive to all sorts of stimuli, and a point may be reached at which it continues to function only because afferent impulses and chemical stimuli together are just able to arouse the sluggish neurons to activity. If now an important group of afferent impulses is suddenly cut off—as by section of the vagus or sinus nerves, or deeper anesthesia—breathing may stop entirely.

Reflexes from contracting muscles probably are responsible for the hyperpnea of muscular exercise. As we shall see (page 604) this is the most vigorous hyperpnea of which man is capable, so that the importance of a reflex factor such as this must be rated correspondingly.

CHAPTER XLI

THE INTERPLAY BETWEEN NERVOUS AND CHEMICAL FACTORS IN THE REGULATION OF RESPIRATION

The course of events in the respiratory center during quiet breathing appears to be as follows: in the interval following the preceding discharge the inspiratory cells of the center, by reason of the oxidative reactions occurring within them, become progressively more excitable until the equilibrium in one or more of them becomes too unstable to be maintained any longer, and when it topples a burst of impulses results. These impulses spread through the reticular formation and all of the cells that are sufficiently excitable (unstable), or are adequately affected, respond to this disturbance by also discharging bursts over their axons. Thus the diaphragm, external intercostals, abductors of the vocal cords, and any other muscles that are involved in quiet breathing, are activated simultaneously, and by each axon leading from the medullary center a number of anterior horn cells may be activated—a "high step-up ratio" (Gesell). All this could be brought about by the discharge from a single reticular cell, and the pace for the entire system (i.e., the *rate* of breathing) could be set by that cell (or group of cells) which most rapidly attains the excitability requisite for a spontaneous discharge of impulses under resting conditions.

The chemical stimulus (which—following Krogh[95]—we shall identify as carbon dioxide acting as such—page 561) presumably acts as a stimulant drug would, namely by combining with the protoplasm of the central neurons in some way which furthers the intracellular reactions that bring about excitability in them. An increase in this factor could either hasten the development of excitability in the pace-setting neurons (i.e., those that had previously been most excitable) and thus shorten the interval between breaths, or it could facilitate the development of excitability in neurons that did not previously respond to the excitation wave; among these are the neurons which innervate the accessory inspiratory muscles, and when these come into play there will be an increase in the depth of breathing without any change in the rate. Actual observation (see page 540) indicates that although both of these things happen during hyperpnea, the *depth* of breathing usually increases before the *rate;* as a rule the rate is accelerated only when the expiratory muscles begin to contract vigorously in their phase, and this is seen only after the accessory inspiratory muscles have also become very active during inspiration. It would seem therefore that an increase in the chemical stimulus has more marked effects on those neurons that are inactive during quiet breathing than on those that are active. This could mean either that the excitation wave in the reticular formation has become stronger than before, and thus is able to reach neurons previously untouched by it, or that the neurons connected with the accessory inspiratory and expiratory muscles have become more excitable by reason of an increase in the number of CO_2 molecules within them. At present there is no compelling evidence upon which to choose between these conceptions, and the point has theoretical rather than practical importance.

The inspiratory act can thus be brought about entirely as the result of chemical factors operating in the center, and unless a certain number of carbon

dioxide molecules are present in the neurons of the center the rhythmic discharge of impulses ceases and apnea ensues (see Chapter XLIV). But as soon as inspiration begins, afferent impulses inhibitory to it also begin to reach the medulla from two sources, viz., the inhibito-inspiratory Hering-Breuer stretch receptors, and the pneumotaxic center in the pons. The former are activated by stretching of the alveoli, the latter by conduction of part of the inspiratory discharge from the reticular neurons upward to be relayed down again as an inhibito-inspiratory (= excito-expiratory) influence. The wave of inhibito-inspiratory impulses so aroused increases proportionately with the depth of inspiration, but since these inhibitory impulses can follow but never precede the inspiratory discharge and since the neurons and fibers of the center are nerve tissue and therefore subject to the all-or-none law (page 46), the strength of their discharge, once it has begun, cannot be diminished by such impulses and none of the inspiratory neurons that are going to respond will be kept by them from doing so. Thus these reflexes can terminate inspiration abruptly and prevent after-discharge or rapid reexcitation, but they cannot keep the depth of breathing from increasing as the chemical stimulus rises. *Depth of respiration therefore depends directly on the strength of the chemical stimulus and the sensitivity of the neurons to it.*

Inspiration comes to an abrupt close for three reasons: first, because the movement of fresh air into the alveoli reduces the CO_2 tension therein and thus decreases the chemical stimulus to the center; second, because the inspiratory neurons, once they have discharged impulses, are relatively inexcitable for a time, even if the chemical stimulus is not reduced, and since they acted in unison they also become inexcitable in unison; third, because the wave of inhibito-inspiratory impulses referred to above reaches its peak at the end of inspiration and therefore becomes stronger as the forces impelling inspiration become weaker. These inhibito-inspiratory impulses may act (as Adrian has suggested) by curtailing the discharge from the inspiratory neurons, thus shortening their phase of activity, bringing on their resting period more quickly and making it more complete, or (as Pitts believes) by increasing synaptic resistance in the reticular formation, thereby preventing repetitive discharge in closed circuits. In either case the end result is to permit the neurons to have a period of rest and recuperation after they have discharged impulses.* According to either conception, an inhibito-inspiratory discharge persisting throughout the respiratory cycle (as in rapid shallow breathing with the chest near the inspiratory position) would be harmful to the center, either because of interference with recovery processes by inhibitory impulses reaching the neurons during their resting phase (Adrian), or because a stronger motor discharge would be necessary to overcome increased synaptic resistance and the amount of energy required to prepare the neurons for this would be greater than would be the case otherwise (Pitts).

When inspiration ceases the neurons connected with the *expiratory* muscles are immediately released from the inhibitory influence exerted upon them by

*It is possible that adequacy of the inhibito-inspiratory reflex factor is largely or wholly responsible for the satisfaction that attends the inspiratory act during quiet normal breathing. The significance of this suggestion will be more evident when we come to consider dyspnea (page 648). At this time it may be well to point out that lack of satisfaction of the urge to breathe, even by the deepest inspiratory effort, constitutes the major difference between dyspnea (in which the act of breathing obtrudes unpleasantly upon the consciousness) and eupnea, or quiet breathing (in which it does not). Effective inhibition of the activity of the inspiratory neurons at the end of each inspiratory effort could certainly account for the latter and lack of it for the former, but the reader should understand that this is only a suggestion.

impulses from the inspiratory neurons (page 557). During quiet breathing the expiratory neurons apparently are not excitable enough, or are not sufficiently affected by the excito-expiratory impulses in the reticular formation, to produce an effective contraction of the expiratory muscles when this occurs, and the lungs simply empty gently by reason of the elastic recoil of the thoracic structures (muscles, ligaments, lungs) and the force of atmospheric pressure exerted upon the chest. This peaceful situation can be altered (as usual in respiration) either by nervous or chemical influences. Assuming that carbon dioxide is the specific chemical agent for the expiratory as well as inspiratory neurons, we may conclude that an increase in the tension of this gas in the blood causes an increase in the number of molecules of CO_2 in the expiratory neurons and therefore an increase in the intracellular reactions that make these cells excitable: when their excitability becomes sufficiently great a discharge of impulses to the expiratory muscles will occur whenever the inspiratory discharge ceases, and expiration then becomes an active process. Among the nervous influences that directly affect the expiratory neurons, special place must be given to those aroused by irritation of the expiratory passages (cough); these constitute a protective device that functions not only in the conscious subject, but in the anesthetized as well. It is probably for this reason that breathing remains vigorous under ether anesthesia although the response of the center to chemical factors is greatly depressed and chemoreceptor reflexes are less effective than under any other type of anesthesia; active expiratory efforts aroused by the irritant effects of the ether vapor replace these other mechanisms under such circumstances, and the relative safety of ether as an anesthetic indicates the adequacy of the replacement. Active contractions of the expiratory muscles, no matter how they are induced, are likely to lead to collapse of the alveoli sufficient to stimulate the expiratory Hering-Breuer receptors and give rise to a burst of excito-inspiratory impulses. This accounts for the fact that the rate of breathing is accelerated in dyspnea, for active contractions of expiratory muscles are a characteristic feature of dyspnea, and the expiratory phase of breathing is definitely shortened when the act is accomplished by vigorous muscular movements. In this way an increase in the chemical stimulus will increase the rate of breathing as well as its depth. Under pathological circumstances this excito-inspiratory discharge is not limited to the stage of deflation of the lungs but is persistent throughout the cycle; if this influence is sufficiently strong (i.e., if enough of the corresponding receptors are involved) the urge to breathe will persist throughout the respiratory cycle (since inspiration does not abolish it) and dyspnea ensues (page 648).

This brings us to a general consideration of excitatory nervous influences that are not in phase with the respiratory act, which includes all those items

TABLE XXI

RESPIRATORY RESPONSES TO EXERCISE*

	O_2 UPTAKE L./MIN.	PULMONARY VENT. L./MIN.	ARTERIAL pCO_2	ARTERIAL pH
At rest	0.25	5	39.8	7.41
Exercise	2.25	42	38.5	7.39
Exercise	3.0	62	37.0	7.43
Exercise	3.25	78	34.0	7.44
Exercise	3.6	118	29.0	—

*These data are derived from Fig. 27 of the paper by Nielsen.[118]

that are classified as "changes in excitability of the center to its normal stimulus" until something is learned about how this (which is obviously the result of something else) is brought about.

As an illustration of the magnitude of this factor Table XXI shows the results of an experiment by Nielsen[118] on a trained subject during exercise (on a stationary bicycle) of increasing intensity. From this and from many similar experiments, by Nielsen and by others, we can safely conclude that the respiratory adjustment to muscular exercise (which is certainly the commonest and probably the most important of all respiratory adjustments) can be secured without any increase, or with an actual decrease, in the carbon dioxide tension and hydrion concentration of the arterial blood. The only other identifiable chemical stimulus which could be held accountable for such a hyperpnea is oxygen-lack, but this cannot be the explanation here, first because the hyperpnea of exercise is much stronger than any that can be produced by carbon dioxide inhalation[119] whereas that of anoxemia is much weaker (page 565), and second, because actual studies of the arterial blood during moderate exercise (see Table XX, page 594) have shown no appreciable anoxemia. It is true that during very intense exercise some anoxemia may be present in spite of the most violent hyperpnea, but this occurs only at oxygen uptakes higher than 4 liters per minute.[120*]

If the extent to which pulmonary ventilation can be altered is any criterion of importance, the question now confronting us is by far the most important one in respiratory physiology. We have already seen (page 565) that the pulmonary ventilation elicited by muscular exercise is much stronger than the maximum obtainable by carbon dioxide inhalation. Barcroft and Margaria[18] found that the magnitude of the two hyperpneas is approximately in the ratio of 2:1; yet the subjects were much more uncomfortable (dyspneic) while breathing air enriched by CO_2 than during the hyperpnea of exercise, even though the latter was double the magnitude of the former. In Nielsen's experiments[119] the maximum pulmonary ventilation obtainable with CO_2 inhalation (50-60 liters per minute) was also about double that observed in the same subjects while exercising (110-120 liters per minute[118]). Yet the stronger hyperpnea of exercise may occur with no increase, or with an actual decrease, in any identifiable chemical stimulus in the blood (Table XXI). In some cases there may be an increase in one stimulus, such as the increased acidity (decrease of pH 0.074) of arterial blood noted in Table XX during exercise, and it is possible that the increase in respiration was due to this factor. It must, however, be remembered that an acid shift greater than this (pH 0.08) may produce only a slight (0.3 liter per minute) increase in respiration, or none at all, when it is brought about by the ingestion of ammonium chloride by resting subjects (page 560). It is much more probable that something other than any of the known chemical factors dominates respiratory control during exercise and that this factor is capable of stimulating respiration so markedly that the increased need for pulmonary ventilation consequent on the increased metabolic activity is completely satisfied. Until recently this factor could not be identified except

*It is inconceivable that results such as those depicted in Table XXI could have been due to accumulation of acid within the respiratory neurons, for these subjects were in a "steady state" at each level of exercise, and if equilibrium between the neurons and the arterial blood was not present here the permeability of the membranes to the stimuli must be so poor as to preclude any possibility that the respiratory center can serve a useful purpose in regulating the neutrality of the body (page 641).

by its result, which is to make the center more sensitive to the chemical stimulus;[118] this is exactly the same conclusion that was applied for many years to the hyperpnea of anoxemia. Just as the latter is now known to be due to the inauguration or augmentation of excitatory reflexes from the chemoreceptors (page 587), so the hyperpnea of muscular exercise, according to evidence submitted by Harrison and his collaborators,[70] is also due to excitatory reflexes aroused in the contracting muscles.

These investigators, like others who have studied this problem before and since, found that the hyperpnea of muscular exercise in man could not be explained by any demonstrable chemical change in the arterial blood. They also found that breathing was promptly stimulated by muscular movements of the hand even though the circulation was cut off by means of an inflatable bandage; this indicated strongly that a chemical product of muscular activity was not responsible, but it was still possible for some such product to enter the general circulation by way of the circulation in the bones. To eliminate this possibility they turned to experiments on anesthetized dogs, in which breathing was found to be stimulated when one hind leg was moved passively, even though the femur was severed, the femoral vessels clamped, and the leg connected with the body only by the sciatic nerve; when the nerve was cut, movements of the leg had no effect on breathing whether the femoral vessels were closed or open. These experiments show, not only that the factor responsible for the observed hyperpnea was not a chemical one acting on the center, but also that it was brought into action by movement of the affected limb; its absence after section of the nerve identifies it as a reflex; the fact that breathing was stimulated when the leg was moved passively indicates that irradiation of impulses from the higher motor centers into the medullary reticular formation was not responsible. Alam and Smirk[6] have recently made analogous observations (on man) with regard to the increase in blood pressure and pulse rate associated with exercise and have come to the same conclusion, i.e., that these physiological adjustments are also brought about by reflexes aroused in the exercising limb, though the reflexes they studied were probably evoked by chemical factors and, therefore, were different from those described by Harrison.

The hyperpnea of muscular exercise differs from others of reflex origin in several important respects: (1) it is associated with an increased production of CO_2, and while pulmonary ventilation usually increases sufficiently to prevent any rise in the CO_2 tension of arterial blood, there is no significant reduction as there is in other reflex hyperpneas; this is probably one of the major reasons why the hyperpnea of exercise is more vigorous than any that can be elicited by other reflex factors; (2) it may be associated with an increase in body temperature, which is another possible factor contributing to the vigor of the response; (3) it usually means voluntary mobilization of large masses of muscles, and while irradiation of impulses from the motor cortex into the reticular formation has been shown by Harrison[70] not to be entirely responsible, this cannot be ruled out as a contributing factor. According to Nielsen and Hansen,[120] the limiting factor in muscular exercise is the circulation, not the respiration; when muscular activity is carried to the limit of tolerance the available supply of oxygen carried by the blood is insufficient to meet the needs of the muscles and as a result of the "oxygen debt" thus contracted fixed acids

accumulate in the muscles and in the blood. The latter may then become acid enough to stimulate the chemoreceptors, thus bringing into play another factor that contributes to the hyperpnea; the same can be said of the arterial anoxemia that may result from very strenuous exercise.

The reflexes from the chemoreceptors of the carotid and aortic bodies may be regarded as the prototype of an excitatory nerve influence operating throughout the respiratory cycle. These reflexes have been studied sufficiently to establish the following characteristics of the hyperpnea so produced: When the stimulus is maximal, there is an increase in both rate and depth of breathing, but ordinarily only depth is increased; the hyperpnea is usually not so intense as that produced by CO_2 inhalation, but this may be only because the CO_2 tension of the blood is reduced by such a reflex hyperpnea and the excitability of the center is thereby diminished. The excitatory nerve impulses simply replace the chemical stimulus as the dominant factor in respiratory control. Just how this is done is unknown, but the proximity of the respiratory center to the nuclei of the glossopharyngeal and vagus nerves, for which the impulses carried from the carotid and aortic bodies apparently are destined, suggests that a set of strong excitatory impulses reaching this region might be able to create a disturbance in the adjacent reticular formation. As a matter of fact, impulses from the chemoreceptors can (in reactive animals) spread out so as to involve not only the medullary centers (respiratory, vasomotor, vomiting), but also motor nuclei, and violent generalized convulsions may ensue; these cease instantly when the chemoreceptor stimulation is terminated (Schmidt[138]—experiments on decerebrated cats).

Thus we emerge with a picture of the balance of direct chemical and nervous control of breathing that is very different from that which was almost universally held until recently. The adjustment of pulmonary ventilation to meet the changing requirements of the body for a supply of oxygen and the removal of carbon dioxide, under ordinary physiological conditions such as muscular exercise and the commonest emergencies such as anoxemia and acidosis, is brought about, not by a change in the chemical stimulus, but by the intervention of a new neurogenic factor which, in the case of anoxemia (and perhaps acidosis also), can be identified with certainty as afferent excitatory impulses from the chemoreceptors of the carotid and aortic bodies, but which, in the case of muscular exercise, can be characterized only by its result, which is to replace the chemical stimulus or—as it is commonly expressed—to increase the excitability of the center to that stimulus. There is no doubt that breathing can be stimulated by an increase in the chemical stimulus (carbon dioxide) in the blood when such increase is brought about intentionally in the laboratory, but there are no ordinary physiological emergencies under which this occurs and the response of the center to inhalations of carbon dioxide may therefore be a laboratory curiosity. The role of the chemical stimulus now appears to be to keep the central neurons in a state of optimum excitability with respect to neurogenic factors; until recently the general belief was that the relation is exactly the reverse of this, the neurogenic factors serving to keep the center properly oriented with respect to the chemical stimulus. Changes in the chemical composition of the arterial blood, as encountered under most physiological and many pathological conditions, are now to be regarded as results rather than causes of changes in pulmonary ventilation.

THE PART PLAYED BY CEREBRAL VASCULAR CHANGES IN RESPIRATORY CONTROL

Since it is probable that some peculiar respiratory phenomena owe their origin to changes in the tone of the blood vessels supplying part or all of the brain, before proceeding with a consideration of respiratory control under abnormal conditions we will do well to consider the possible relation of the cerebral circulation to the regulation of breathing. We have already seen (page 579) that the respiration of an anesthetized animal may, under favorable conditions, be shown to be subject to modification by altering the blood supply of the brain, and have indicated that such modifications of breathing are probably due to corresponding changes in the extent to which stimulant products of the metabolism of the cells of the center are permitted to accumulate there. It is to be hoped that the reader did not fail to note the statement (page 579) that changes such as this have little or no clinical importance. That, however, is not the case with the changes in the cerebral circulation that can be produced, presumably in the finer vessels, by experimentally induced changes in the chemical composition of the blood and (by inference) by certain disease conditions. This is a subject about which nothing was known until recently and although our knowledge is still far from complete it is now possible to draw at least a tentative picture of the factors involved.

The intrinsic control of the blood vessels supplying various parts of the brain can be shown to be brought into play either by changes in the carbon dioxide tension in the arterial blood, an increase in tension producing an increase in blood flow, a decrease, a diminution in flow (changes which involve the entire central nervous system), or by an increase in the local metabolism associated with increased functional activity, as evidenced by an increase in blood flow in the visual cortex when light is flashed into the eye (Fig. 241). Since this particular result was obtained in a part of the brain in which (so far as is known) there is no effective vasomotor nerve control, it is most probably due to the direct effect of the increased local CO_2 production resulting from the illumination. This necessitates the further conclusion that the effect must have been exerted upon capillaries rather than arteries, since only the former are permeable enough for the caliber of the vessels to be directly affected by changes in the CO_2 tension in the tissue surrounding them. In most other parts of the body the normal intrinsic control is accomplished mainly if not entirely by changes in tone of the muscle of the arterioles under the influence of impulses carried from the vasomotor center, and when these impulses are lacking the vessels dilate. In the brain, although vasomotor nerves are known to be present and can be shown by artificial stimuli to be capable of eliciting definite effects in some parts of the organ, these effects are different in important respects from those produced by corresponding vasomotor nerve stimulation in other regions of the body and are probably not to be regarded as evidence in favor of a normal vasomotor nerve control of cerebral blood vessels. This conclusion is borne out by the failure of cerebral blood flow to increase when the cervical sympathetic nerves are cut although flow in extracranial parts of the cephalic circulation (temporal or mylohyoid muscle, tongue) increases markedly (Schmidt and Hendrix,[144]). The intrinsic regulation of the circulation in the brain seems to differ from that elsewhere in the body in these important respects: in the brain the vessels possess a high intrinsic tone and their normal control depends on the extent to which they are kept from going into a state of excessive constriction (spasm) by chemical vasodilator agents, particularly carbon dioxide. In most other tissues the regulation depends on the extent to which tone is conferred by vasomotor nerve impulses upon vessels otherwise devoid of it; the vasodilator action of carbon dioxide on cerebral vessels probably is exerted upon the finest, most permeable ones (capillaries) while elsewhere the vasomotor control is necessarily strongest where smooth muscle is best developed (arteries, arterioles). This organization is well suited to the maintenance of constancy in the chemical state within brain cells in the face of changes in their own metabolic activity and in the chemical composition of the blood, which would not be the case if the

cerebral vessels were markedly influenced by vasomotor nerve impulses. In the coronary circulation the general arrangement appears to be very similar to that in the brain (page 506). Since the brain and the heart are the most susceptible of all body tissues to derangement by lack of oxygen, this organization was probably developed by a process of natural selection in which, among countless varieties of animals possessing innumerable types of vasomotor control, only those individuals whose cerebral and coronary arteries were not constricted by vasomotor nerve impulses survived emergencies such as violent exertion, emotions, struggle, flight, submersion, etc., to bear progeny that were similarly organized. *The brain and the heart apparently are too precious to the organism to be subjected to the caprices of the vasomotor center.*

Fig. 241.—Effect of illuminating eye on blood flow in visual cortex.

Cat—pentobarbital anesthesia, curare, artificial respiration. *Upper record*, blood flow in mesial surface of occipital lobe (registered by a small, cooled thermocouple inserted directly into the tissue). *Next record*—femoral blood pressure. Time tracing shows 5-second intervals. Between signal marks light from a small flashlight was flashed into opposite eye (previously protected from light). (From Schmidt and Hendrix: Proc. A. Research Nerv. & Ment. Dis. **18**: 229, 1938.)

Applying these deductions from experimental observations to the regulation of respiration, we may suppose that changes in tone of the finer vessels supplying the central neurons help to keep constant the number of molecules of carbon dioxide within them and thus to minimize the response of the respiratory center to changes in the chemical composition of the blood. The importance of this factor in the control of breathing under normal circumstances is problematical, but under certain abnormal conditions it can become very important. Perhaps the simplest of these is voluntary hyperpnea, by which—if it were sufficiently intense—one might expect the CO_2 tension of the blood to be so markedly reduced that the cells of the center would be completely inactivated for a dangerously long time. What is likely actually to happen when a vigorous subject makes an attempt to produce a maximal reduction in his arterial CO_2 in this way is the onset of complete unconsciousness within a few minutes, and with it the will to breathe is also lost, so that apnea ensues. After a brief interval (a minute or less) consciousness gradually returns and breathing is resumed, weakly at first, then more and more strongly until the full hyperpnea is again evident. This gives way once more to loss of consciousness and apnea. In this way a vigorous normal subject can produce perfectly typical Cheyne-Stokes respiration (page 656) in himself. These phenomena are not dependent upon a fall in blood pressure, for pressure may be unchanged or it may rise slightly, but it does not fall significantly. They are not due to fatigue, for they do not occur if alveolar air or 5 per cent CO_2 in air is breathed instead of room air: in such cases consciousness remains unclouded, the hyperpnea persists without interruption, and no periodicity appears. They are not due simply to the direct influence of the altered chemical composition of the blood upon the respiratory center, for if a vasodilator drug such as nitroglycerin is given beforehand, the result is the same as though CO_2 had been added to the inspired air (i.e., no periodicity), although the chemical changes produced in the blood by the hyperpnea would not be modified by this drug. Since nitroglycerin is one of the most effective of cerebral vasodilators,[144] we are justified in attempting to explain the above observations in terms of changes in the finer cerebral vessels consequent upon the voluntary hyperpnea. The course of events is probably as follows: as the CO_2 tension of the arterial blood is reduced by the hyperpnea the cerebral vessels constrict progressively until the cortical cells that are most susceptible to anoxia (those concerned with consciousness—see page 655) become incapacitated and consciousness is lost. Since the dominant factor in respiratory control—the will to breathe maximally—had come from these cells, and since the chemical stimulus to the respiratory center was greatly reduced by the voluntary hyperpnea, breathing diminishes progressively as consciousness is lost and it soon ceases entirely. During this period of apnea the subject is completely unconscious, does not respond to various stimuli—even to pain—and cannot be made to breathe. Meanwhile CO_2 accumulates, the cortical vessels begin to dilate, consciousness returns, and breathing begins again. During this phase the subject is perfectly conscious and will stop the hyperpnea instantly when requested to do so, but if that is not done another cycle of unconsciousness and apnea ensues, and so on.

In such cases there seems little doubt that the primary factor is periodic cessation of volitional hyperpnea consequent upon periodic unconsciousness, this

resulting from constriction of cortical vessels produced by reduction in the CO_2 tension of the arterial blood. Cyclical constriction of the blood vessels supplying only the respiratory center need not be called upon to explain the Cheyne-Stokes breathing thus produced. As encountered clinically, however, periodic breathing can frequently be made regular by cerebral vasodilator drugs (theophylline, or choline derivatives, page 658). Since there is no reason here to suspect that impulses from cortical cells are essential to the maintenance of breathing, it is most likely that the fundamental factor in such cases is an increased tone (spasm) of the vessels in the entire brain, including the respiratory center, that periodic relaxation of these by accumulation of CO_2 during the apneic period causes return of breathing and improvement of consciousness (in most cases), and that prolonged dilatation of the vessels by drugs causes return of continuous breathing and improvement in consciousness because a preexisting anoxic depression due to spasm of these vessels is now relieved. Why there should be a tendency toward spasm of cerebral vessels in such cases (or indeed the fact of its occurrence) remains to be determined. The coincidence of loss of consciousness, fall in blood pressure, and apnea which usually exists in Cheyne-Stokes breathing in man (page 657) suggests that the neurons of the cortex, the vasomotor center, and the respiratory center are all depressed simultaneously as a result of the spasm.

If it is true that constriction of cerebral vessels sufficiently intense to cause anoxia within brain cells can be produced by reduction in the CO_2 tension in the blood, it follows that cerebral anoxia is likely to be produced by any reflex hyperpnea. Since one of the most important causes of reflex hyperpnea is anoxemia, it follows that here (as in any physiological manifestation of anoxia) a vicious circle is set up; the hyperpnea causes reduction in the CO_2 tension of the arterial blood and since (as far as is now known) the influence of CO_2 on the cerebral vessels is stronger than that of anoxemia, they then constrict, thus adding to the anoxia already imposed upon the brain by the reduction in blood oxygen tension that induced the hyperpnea. At the same time the chemical stimulus to the respiratory center is decreased by reason of reduction in the CO_2 tension of the blood; this helps to diminish the hyperpnea and thus to weaken the most effective compensation for reduction in the oxygen tension in the inspired air (see Chapter XLV). If we add to this the possibility that chemoreceptor reflexes may have widespread stimulant effects on the central nervous system (page 606), it becomes probable that sudden relief of an anoxemia of considerable duration may have unexpectedly bad effects, such as unconsciousness, fall in blood pressure, and—if the neurons had been severely damaged by anoxia—respiratory failure and death. The latter may be responsible for an occasional fatal result from tracheotomy (page 664). Perhaps certain airplane crashes that have been blamed on plane failure were actually due to pilot failure brought about in this way, for it is known[115] that the beginning or resumption of oxygen inhalation at a high altitude sometimes causes unconsciousness and fall in blood pressure; this probably means that the reflex stimulus set up by anoxemia had been the dominant factor in maintaining the activity of the entire neuraxis, and when this is suddenly removed severe depression (perhaps contributed to by spasm of cerebral blood vessels) promptly ensues.[141]

Under abnormal conditions such as shock, hemorrhage, anoxemia, and (of special importance) anesthesia, the cerebral vessels dilate and their ability to respond to various influences is weakened or lost. The degree of this effect varies among different narcotics, being perhaps greatest with ether, but as far as is known it is elicited to some extent by all narcotics and in proportion to the severity of the poisoning. This may be viewed as a compensatory process, intended to increase the available oxygen supply to the brain cells when their ability to utilize oxygen is interfered with by the narcotic. But if it is true (as we have assumed above) that the tone of the finer cerebral vessels is normally altered in an attempt to maintain constant the chemical composition (particularly CO_2 tension) of the respiratory neurons, this adjustment must be interfered with by narcosis and the chemical stimulus to these cells should then be subject to greater fluctuations than would normally be the case. That this is true can be shown quite clearly in the case of the vasomotor center: in normal, unanesthetized human subjects who overbreathe voluntarily blood pressure does not fall, presumably because the chemical stimulus to the vasomotor neurons is kept, by constriction of the blood vessels supplying them, from falling dangerously, but in anesthetized men[147] a relatively small grade of overventilation causes quite marked fall in blood pressure, indicating that this protective mechanism is no longer effective.

CORRELATION OF THE GENERAL CIRCULATORY AND THE RESPIRATORY RESPONSES

As a rule the most powerful influences that affect the respiratory center affect the vasomotor and cardioaccelerator centers at the same time and in the same direction. If we accept Kapper's[90] conception of the reasons for the existence of a reticular formation (page 553) and take the viewpoint that the medullary reticular formation is organized around impulses carried from the viscera by the glossopharyngeal and vagus nerves, for the purpose of coordinating the muscular movements involved in the respiratory gas exchange with the environment, we can expect that various cells scattered in this region are connected to the respiratory muscles, the blood vessels, and the heart, thus constituting parts of the corresponding centers but with little or no special localization. That the wave of excitation sweeping over this region at inspiration involves the vasomotor and cardioaccelerator neurons is shown by the tendency of the impulses carried by the corresponding nerves to be grouped (like those to the respiratory muscles) in bursts synchronous with inspiration (Bronk). Applying to this organization the general conception that we have already applied to the adjustment of the respiratory movements to meet changing requirements (page 554), we can conclude that the number of cells discharging impulses over vasomotor and cardioaccelerator nerves will increase with the strength of the stimuli, nervous and chemical, and that these stimuli are in the main identical with those concerned in the control of respiration.

We may then conclude that the various neurons of the reticular formation, by responding to changes in the strength of the chemical stimulus brought to them by the blood or produced by their own metabolism, and to changes in the

balance among excitatory and inhibitory nerve impulses that constantly play upon them, can bring about changes in pulmonary ventilation and in blood flow through the brain that will produce an opposing change in the chemical state within these cells and thus restore to them the balance of affairs most to their liking. In so doing the chemical composition of the arterial blood and the circulation through tissues under vasomotor nerve control are modified to suit the desires of these cells in the medulla. Thus we can understand why the circulation and the respiration are both stimulated by an increase in the CO_2 tension in the blood, though here the rise in blood pressure produced by increased vasomotor activity may be more or less effectively opposed by the vasodilator action of CO_2 (page 475) and the hypertension therefore is not as conspicuous as the hyperpnea. We can also understand why afferent impulses from the carotid and aortic chemoreceptors stimulate the respiratory, vasomotor, and cardioaccelerator centers simultaneously, as shown by the hyperpnea, hypertension, and tachycardia elicited by acute anoxemia (page 676).

From this point of view special interest must be attached to the observations of Alam and Smirk[6] who found that a very considerable rise in blood pressure and acceleration of the heart rate occurred in normal human subjects when they were made to contract voluntarily a group of muscles (leg, forearm, even a little finger) whose blood supply was intentionally restricted. Since these effects did not ensue in the absence of circulatory restriction, they were not due to purely emotional or psychic factors, and they were not necessarily associated with pain. The authors interpret their observations as indicative of a reflex influence, aroused in muscles by accumulation there of metabolic products, and capable of producing powerful stimulant effects on the vasomotor and cardioaccelerator centers.

This conception has obvious and direct applications to the physiology of muscular exercise. According to recent evidence[10] the increased circulation required by an exercising muscle, secured mainly by an increase in the capillary bed therein, is not brought about until the exercise has continued for some time. Meanwhile the oxygen supply of the muscles is relatively inadequate and acid products of incomplete oxidation (such as lactic acid) appear in the blood stream, indicating considerable accumulation of such materials in the exercising muscles; the situation would then be essentially similar to that in the experiments of Alam and Smirk. When the circulatory readjustments in the exercising muscles become effective, the lactic acid of the blood diminishes toward or to normal even though the exercise is continued[10] and the "oxygen debt" contracted in the earlier stages is paid off; the subject now is in a "steady state" and the exercise entails less discomfort than before. This explains the well-recognized benefits derived from "warming up" before indulging in strenuous exercise.

The work of Harrison and his associates[70] indicates that reflexes similar to those described by Alam and Smirk affect the respiratory neurons in the same direction and at the same time as the vasomotor and cardioaccelerator system. We have just seen (page 604) that the hyperpnea of exercise can now, with some confidence, be attributed to a set of afferent impulses aroused in suitable receptors in the exercising muscles; these might be excited by changes in length or by products of the muscle's own metabolism. In the latter event the well-known phenomenon of "second wind" might be attributed to the onset of a

"steady state" by reason of vascular readjustments capable of meeting the increased demands of the muscles for oxygen, thus reducing the intensity of this reflex drive on the respiratory neurons; perhaps accumulation of lactic acid in the blood in the earlier stages and its disappearance subsequently (because of the same vascular phenomena in the muscles) acts through the carotid and aortic chemoreceptors as an additional factor in the same direction.

The reader should clearly understand that any such relation of the respiratory phenomena associated with muscular exercise to reflexes aroused in the muscles by metabolic products is at present entirely speculative. Further investigation seems very desirable.

CHAPTER XLII

THE GAS EXCHANGE IN THE LUNGS

The respiratory movements are the mechanical devices which enable the body to call upon the external environment (air) for a supply of oxygen and for the removal of CO_2. We have considered the nature of the respiratory movements and their regulation. The next step in the respiratory process is the gas exchange in the lungs, and we shall now inquire into the factors concerned in the uptake of oxygen by, and the removal of CO_2 from, the venous blood in its passage through the lungs.

The average normal adult consumes about 250 ml. of oxygen and produces about 200 ml. of CO_2 per minute when at rest. Any increase in activity increases the metabolism proportionately, and during strenuous exercise the above figures may be increased as much as twenty fold. All the oxygen consumed and all the CO_2 produced must pass through the membranes which separate the blood from the air in the lungs, and the process must occur very rapidly because the blood traverses the pulmonary circulation in one second or less. The interchange of gases takes place between the alveolar air and the venous blood which reaches the pulmonary capillaries from the right ventricle; the blood takes up oxygen and gives off CO_2, emerging from the lungs to enter the left auricle as arterial blood. The oxygen and CO_2 content of the atmospheric air, alveolar air, and blood in milliliters per 100 are approximately as follows (at sea level, and in a normal adult at rest):

	ATMOSPHERE	ALVEOLAR AIR	VENOUS BLOOD	ARTERIAL BLOOD
Oxygen	20.90	14.0	15	20
CO_2	0.03	5.6	52	48

During exercise the venous blood may contain as little as 5 ml. of oxygen and as much as 65 ml. of CO_2 per 100, but the arterial blood still emerges with practically the same amounts of these gases as it does when the subject is at rest. The rate of movement of air in and out of the lungs is increased during exercise, and this carries more fresh air into contact with the alveoli. But at the same time the rate at which the blood flows through the pulmonary capillaries may be increased as much as fivefold; if there were not an ample margin of safety in the provisions of nature for transferring the gases between air and blood the arterial blood would approach the venous in gas content during exercise and the result would be the same as that of strangling or drowning. It has been estimated that this margin of safety is about 100 per cent, meaning that half of the normal pulmonary surface is sufficient for the resting needs of the body.*

The transfer of the gases between the blood and the alveolar air is accomplished by diffusion, which means passage of the gas molecules from a place at which the pressure (tension) of the gas is higher to one at which it is lower.

*Graham (Surgery 8: 239, 1940) has recently reported survival of a young man after removal of four of the six pulmonary lobes; he believes that one-eighth of the total pulmonary tissue would suffice for the needs of the body under resting conditions.

The tensions of the gases involved in the respiratory exchange, in millimeters of mercury and in a normal resting adult at sea level, are as follows:

	INSPIRED AIR	ALVEOLAR AIR	VENOUS BLOOD	ARTERIAL BLOOD
Oxygen	159.00	100	40	90
CO_2	0.23	40	46	40

Before we proceed further with a consideration of the pulmonary gas exchange, we may profitably review those physical properties of gases which are concerned in the respiratory gas exchange.

THE GAS LAWS

The behavior of the respiratory gases in the lungs and tissues can be explained on the ground that gases are composed of discrete particles (molecules) constantly in motion in straight lines and with great velocity (kinetic hypothesis). According to this view the pressure or tension of the gas is due to the bombardment of the walls of the vessel which contains it by the constantly moving molecules. Anything that increases the bombardment must therefore increase the tension. The following gas laws express the factors of greatest physiological importance:

1. *For all gases, an equal number of molecules in the same space and at the same temperature will exert the same pressure* (*Avogadro's hypothesis*). It is evident that for two gases whose molecules are of different weight equal numbers of molecules will be obtained by measuring the gases in quantities proportional to their molecular weights. The molecular weight of any gas (referred to $O_2 = 32$) in grams (called a gram-molecule, or, for the sake of brevity, a mol) will occupy, at a temperature of 0° C. and a pressure of 760 mm., a volume of 22.4 liters. A pressure of 760 mm. (one atmosphere) means a pressure of 1033.3 grams per square centimeter, or about 15 pounds per square inch.

2. *As a gas is compressed its pressure increases in exactly the same proportion as its volume diminishes* (*Boyle's Law*). Thus a mol of any gas, when compressed at 0° C. to a volume of one liter, will exert a pressure of 22.4 atmospheres. The molecules now have to move a much shorter distance before they strike the walls of the containing vessel and the pressure is increased accordingly.

3. *Any gas expands when heated and contracts when cooled;* taking the volume at 0° C. as the standard, the gas increases in volume by $\frac{1}{273}$ for every degree C. rise in temperature. This means that if the volume is kept constant the pressure of a given gas is proportional to the temperature (*Law of Gay-Lussac*). Increased temperature increases the speed at which the molecules move, hence the rise in pressure.

One of the most characteristic properties of gases is their ability to diffuse, i.e., to pass from a point of higher pressure to one of lower and to expand and fill the entire available space. According to the kinetic hypothesis, diffusion is the result of the continuous movement of the gas molecules, and since the pressure is believed to afford a measure of that movement, the rate of diffusion is directly proportional to the pressure (Boyle's Law) and temperature (Law of Gay-Lussac); it is inversely proportional to the square root of the density (molecular weight) of the gas (Graham's Law).

When gases are taken up by liquids (as they must be to participate in the gas exchange in the body) the same laws continue to operate, but the situation is modified by the ability of the liquid to absorb or to combine chemically with each gas. This determines the volume of the gases that can be taken up by the liquid at a given temperature and pressure. The volumes (in milliliters per 100) of oxygen, CO_2, and nitrogen that can be dissolved by water, blood plasma, and whole blood, when exposed at 38° C. to an atmosphere of each gas (760 mm. pressure) are as follows:

	WATER	PLASMA	BLOOD
Oxygen	2.37	2.3	2.3
CO_2	55.5	54.1	54.1
Nitrogen	1.2	1.2	1.1

The corresponding volumes dissolved by the blood at the pressures existing in the alveolar air and at 38° C. are approximately:

Oxygen	0.3 ml. per 100 (volumes per cent)
CO_2	3.0 ml. per 100
Nitrogen	0.8 ml. per 100

These are the volumes of the gases taken up by the blood in purely physical solution; the amounts taken up in chemical combination are not included. The latter are much greater than this (see page 627) except for nitrogen, which does not combine chemically with the blood, does not participate in the gas exchange, and is carried entirely in physical solution. The important point is that CO_2 is by far the most soluble of the respired gases, and this is probably responsible for much of the ease with which CO_2 diffuses in the body.

4. *The law of solution of gases in liquids* (*Henry's Law*) states that the weight (i.e., the number of molecules) of a gas absorbed by a given liquid with which it does not combine chemically is directly proportional to the pressure of the gas, other things being equal.

5. *The law of partial pressures of gases dissolved in liquids* has to do with the pressure exerted by individual members of a mixture of gases. If the gases do not react chemically with one another (and none of the respiratory gases do) the partial pressure or tension of each constituent of the mixture is that which it would exert if no other gas were present. The tension of each gas in the liquid is the same as its partial pressure in the gaseous phase; the molecules of each gas move into the liquid until the pressure is equal in the two phases and are kept from leaving the liquid by the pressure existing in the gaseous phase. If the pressure in the latter is increased, more gas molecules pass into the liquid until the pressure in the two phases becomes equal at the higher level, and if it is decreased, gas molecules escape from the liquid until the pressure in the two phases is again equalized at a lower level. *The tension of a gas in a liquid can be regarded as the force with which the gas molecules are constantly striving to escape.* The tensions of the respiratory gases in the blood are due entirely to that portion of each gas which is dissolved in the plasma; the larger amounts carried in chemical combination serve as reservoirs from which additional gas molecules are liberated to pass into the plasma when the tension of the gas is reduced, or in which additional molecules are stored when the tension is increased. Gases in chemical combination do not exert a tension and therefore cannot diffuse.

The tension of a gas is of the utmost importance as regards its physiological effects, for this is the measure of the force which drives its molecules through living membranes and which determines the number of molecules of the gas that will enter and leave the body. The oxygen which enters the body must diffuse from the atmospheric air into the alveolar air, from the alveolar air into the blood, and from the blood into the tissues; the CO_2 which is exhaled must follow the same pathways in the reverse direction. The physical factors which govern the rates of diffusion at each step are: (1) the difference in tension, (2) the solubility of the gas in the blood, (3) the temperature, and (4) the density of the gas. Solubility, temperature and density are constant in a given individual under given conditions, so that the rate of diffusion of gases into and out of the body depends directly and solely upon the tensions of the gases. But to enter or leave the blood and the tissues the gases must traverse living membranes which interpose barriers to the free diffusion of gas molecules. Furthermore, we have so far taken into account only the rate at which the gases diffuse and have said nothing about the size of the surface available for the process in the lungs, though this is obviously a factor of utmost importance in determining the total amount of gas that can enter and leave the body at a given difference in tension between venous blood and alveolar air. The membranes and surfaces involved are those of the lungs and we shall now consider the part played by the tissues of the lungs in the pulmonary gas exchange.

THE PART PLAYED BY THE LUNG IN THE GAS EXCHANGE

Until recent times it was assumed that the lungs behave like passive sacs and that the parts having the thinnest walls—i.e., the alveoli—are the ones which expand and contract as the volume of the thoracic cavity alternately increases and decreases. Observations made by means of the x-rays and the bronchoscope have shown that this is by no means the case. They indicate that the ventilation of the lung involves active changes in that organ and that most of the changes in capacity of the lung with respiration take place in the air passages and not in the

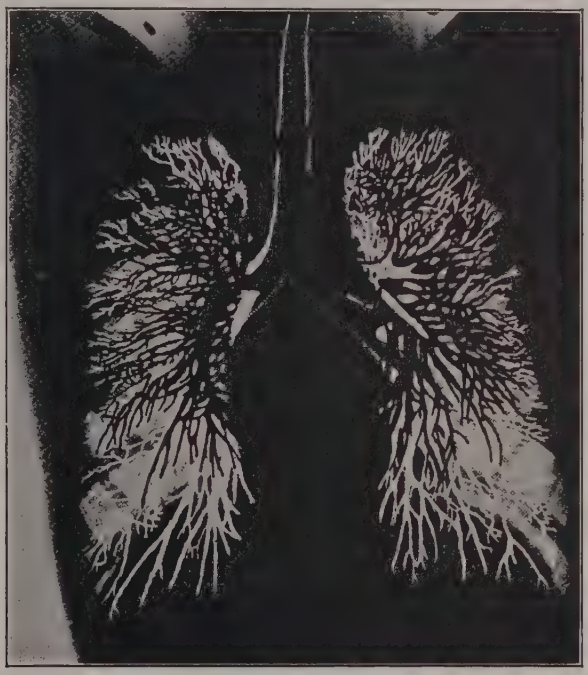


Fig. 242.—Changes in bronchi during the respiratory cycle. X-ray photographs of human lungs superimposed and retouched; expiratory phase in black, inspiratory in white. (From Macklin: Am. J. Anat. 35: 303, 1925.)

alveoli. In order to understand the part played by the lung itself in external respiration, it is necessary to refer to the structure of the organ (see page 547).

The *unit* of the lung is a respiratory bronchiole with the alveolar ducts and alveoli arising from it, together with the corresponding blood vessels, lymphatics, nerves and connective tissue (Maximow[112]). This is the distensible or "bellows" part (Keith), as well as the respiratory part of the structure. These units are found throughout the entire thickness of the lung, as well as on surfaces, such as the mediastinal and posteromedial, and the posterior aspects of the apices, where they cannot be directly expanded by the inspiratory movements of the

thorax. It follows therefore that the alveoli would be very unevenly and unequally ventilated unless there were some special provision for moving air into and out of them. Recent studies have shown that the alveoli are actually ventilated, not by expansion of their walls, but by elongation and expansion of the air passages from which they arise. The alveoli themselves are said to change very little in size during the respiratory cycle; although the lung enlarges in all directions during inspiration and contains a correspondingly increased volume of air, most of the change is in the air passages, and principally in the finest ones—the infundibula of Keith[92] or the alveolar ducts of Macklin.[109]

Changes in the length of the larger air passages can readily be demonstrated roentgenologically (Fig. 242). With inspiration the entire system elongates, the trachea and bronchi move downward, and the root of the lung moves downward and forward. Although the finer passages cannot be visualized so clearly, it is most probable that they too elongate. As a consequence the lung opens up like a concertina, with the difference that the lung comes broader and thicker as well as longer (Macklin[109]). The deeper the inspiration, the greater is the elongation of the bronchial tree. With inspiration the air passages become not only longer but also wider. This can be seen in the larger passages with the bronchoscope, and the finer ducts, including the orifices from which the air enters the alveolar sacs and alveoli, doubtless behave similarly. The elongation is due to the outward pull exerted by the movement of the thoracic walls away from the lung surfaces; the widening of the passages as they elongate is doubtless due in part to the same cause, but it is probable that the smooth muscle in their walls undergoes a decrease in tone during inspiration (Macklin). With expiration the entire bronchial tree shortens in all directions and the tubes become narrower at the same time. The shortening can be accounted for by recoil of elastic tissue stretched during inspiration; the narrowing implies a return of tone to the smooth muscle of the air passages.

Ventilation of the alveoli appears to be accomplished, not by expanding them as passive sacs and thus sucking in air from the alveolar ducts, but by a lengthening and expansion of the ducts and an increase in the size of the openings into the alveolar sacs (Macklin). Air rushes toward the alveoli during inspiration because the pressure in the air passages is now lower than atmospheric, because the resistance to the onward flow of air is lessened by reason of expansion of the ducts, and because the capacity of the duct system is increased by simultaneous elongation and widening. All these factors vary directly with the depth of breathing. If it is true that the alveoli themselves do not expand the incoming air can be drawn only as far as the alveolar ducts, but the currents set up in the passages by the inflowing stream of air, aided by the inspiratory enlargement of the openings into the air sacs, make possible a free interchange of gases between the ducts and the alveoli. In fact, air currents in the bronchi are capable of sustaining an adequate alveolar ventilation in the absence of all respiratory movements, as Meltzer[116] showed. He found that if a constant current of air or oxygen is supplied under gentle pressure through a catheter inserted in the trachea to the region of its bifurcation an animal can be kept alive for long periods without breathing. This procedure, known as intratracheal insufflation, has come into practical use in operations on the lung or other thoracic contents, and to some extent for purposes of resuscitation.

The *bronchial musculature* plays a part in alveolar ventilation by relaxing with inspiration and regaining its tone with expiration, thus enlarging the air passages as they elongate. Existing evidence indicates that this muscle system is under the control of two sets of nerves, the vagus which is motor, and the sympathetic which is inhibitory. The changes in tone associated with breathing are probably brought about through these nerves, but whether both are concerned or only one, and if the latter, which one, is not known. Anatomical studies indicate that the muscle envelops the openings of the air sacs into the alveolar ducts in a sphincter-like structure, relaxation of which during inspiration would greatly facilitate the ventilation of the alveoli (Macklin[109]). The muscle is most highly developed in the region of the bronchioles, and this is where the movement of air is most likely to be interfered with by excessive tone of the muscle fibers. Such a condition produces *asthma*, which occurs in a variety of diseases, conspicuously in those associated with sensitization to foreign proteins. A number of drugs and poisons may produce bronchial spasm, notably those which are parasympathomimetic (vagomimetic), such as muscarine, choline derivatives, eserine, and pilocarpine, and those which excite smooth muscle irrespective of its innervation, such as morphine and its congeners, and histamine. Bronchial constriction also occurs in anaphylaxis, and Dale[44] suggests that it may actually be due to liberation of histamine from tissues damaged by exposure to the protein to which they are sensitized. Spasm of bronchial muscle is relaxed by sympathomimetic drugs, such as adrenalin and ephedrine; that due to vagomimetic agents is also relaxed by atropine. Asthma is not always due to spasm of bronchial muscle; congestion in the pulmonary circulation, as in cardiac disease, may produce it, probably by pressure on the finer air passages by engorged blood vessels, and chronic inflammatory processes may also impinge on the finer tubes. A number

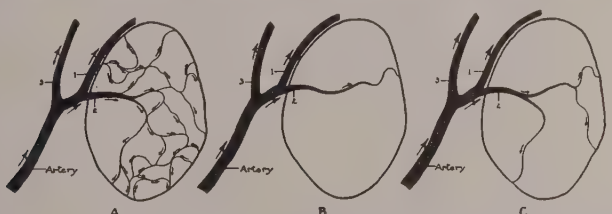


Fig. 243.—Changes in circulation in the wall of an air sac of a cat's lung. Intratracheal insufflation—no respiratory movements. *A*, *B*, and *C* are spontaneous changes: length of capillary channels in *A* is about 3.6 times that in *C* and 9.2 times that in *B*. (From Wearn et al.: Am. J. Physiol. **109**: 236, 1934.)

of observations have been made which indicate that the bronchial musculature is capable of wavelike, peristaltic movements adapted to the extrusion of mucus and foreign material; the factors responsible for such movements are unknown. Perhaps the rhythmic changes in tone of the smooth muscle of the respiratory passages are another manifestation of the organization of the medullary reticular formation and of the dominance of the excitation wave which traverses it at each inspiration; since bursts of impulses having the rhythm of respiration can be found in the vasomotor and cardiac nerves, it is certainly possible that the same rhythm might also extend to this other autonomic innervation. Relaxation of this musculature with the first breath (i.e., with the first excitation wave in the reticular formation) may be necessary to secure inflation of the lungs after birth (see page 674).

The alveolar surfaces of the lungs are well suited to permit free diffusion of gases between blood and air. The two media are separated only by the endothelium of the capillaries and the epithelium of the alveolar walls, there being only a very tenuous supporting framework and, as we have already seen (page 547), there is even some doubt as to the existence of the epithelial layer in the alveolar walls; the barrier to diffusion is about the smallest possible. The surfaces are enormous. Willson[163] has calculated from careful measurements made on a piece of human lung that both lungs, in the position of full inspiration, would have a total air-bearing surface of about 70 square meters. This includes both

nonrespiratory (air passage) and respiratory (alveolar) surfaces, and since there is no means of determining anatomically the relative proportions of the two, he concludes that the alveolar area available for the exchange of gases must be something less than 70 square meters. Gertz[56] estimates the total respiratory area at about 50 square meters while Krogh[95] gives the figure of 90 square meters. The total area of the capillaries in the alveolar walls of the human lungs is stated by Maximow[112] to be 140 square meters. This figure was doubtless obtained by measurement of the vascular area in fully injected dead tissue and must be taken to represent the maximum vascular surface that could be available for the diffusion of gases. The recent studies of Wearn and his co-workers[162] show that the circulation in the alveolar capillaries of the cat is highly variable from moment to moment in the same animal. Capillaries may open and close (Fig. 243), depending upon a regulating mechanism on the arterial side. Excep-

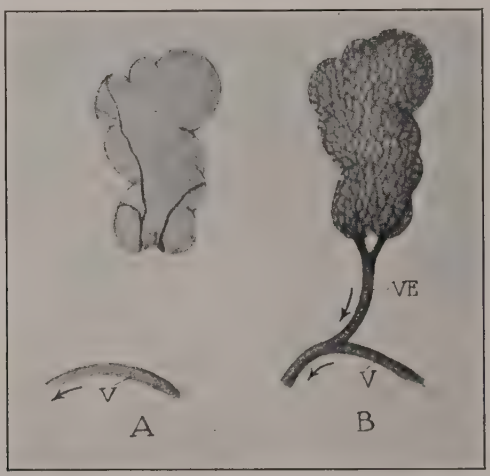


Fig. 244.—Spontaneous opening of entire capillary bed in an air sac of a cat's lung. *A*, only a few capillaries open; *B*, entire capillary bed carrying blood—circulation now failing. *V*, branch of pulmonary vein; *VE*, venule which became visible only as capillaries opened. Magnification ×117. (From Wearn et al.: Am. J. Physiol. **109**: 236, 1934.)

tionally the entire vascular network opens and passes blood (Fig. 244) but the circumstances under which this occurs have not yet been determined; CO_2 excess and oxygen-lack apparently do not have this effect. The part played by this variability in the alveolar circulation in the physiology of respiration is at present unknown. We must at least conclude that of the maximum area (140 square meters) of alveolar capillaries, only a fraction—and probably a small though variable one—is ordinarily utilized in the respiratory act. Even so, the surfaces available for the exchange of gases are enormous.

THE RATE OF DIFFUSION OF THE RESPIRATORY GASES THROUGH THE MEMBRANES OF THE LUNGS

The *diffusion constant* is defined by M. Krogh[96] as *the total number of milliliters of the gas which pass through the entire pulmonary membrane per*

minute for each millimeter difference in tension on the two sides of the membrane (alveolar air and blood). For oxygen the values in normal adult males were found to vary from 23 to 43 during rest and from 37 to 56 during work; in females the corresponding values were somewhat lower (from 22 to 29). Bøje[25] subsequently obtained nearly identical results. Much of the increased rate of diffusion during exercise is attributed to increase in the rate of blood flow through the lungs.* Harrop[71] found diffusion constants for oxygen ranging from 25 to 45 in eight healthy men who were members of Barcroft's expedition to the Andes in Peru (see page 689). The diffusion constant for CO_2 is about 20 to 30 times as great as that for oxygen (A. Krogh[94]), which is another manifestation of the ease with which CO_2 can pass through living membranes.

We have seen (page 614) that the tension of oxygen in the alveolar air is 100 mm. while that in the venous blood is 40 mm. when the subject is at rest, and may be considerably lower when he is exercising. The difference in tension of oxygen on the two sides of the membrane is therefore 60 mm. when the subject is at rest and higher when his oxygen consumption increases. Even with a diffusion constant of 23, enough oxygen could diffuse into the blood to furnish $23 \times 60 = 1380$ ml. of oxygen per minute, and with the same difference in tension (60 mm.) but the higher diffusion constant (56) during exercise, 3360 ml. of oxygen could diffuse per minute. The largest oxygen consumptions recorded in man lie between 4,000 and 5,000 ml. per minute, and these are unusually high. Under such circumstances the venous blood would certainly have a lower oxygen tension than 40 mm., and the difference in tension of oxygen between alveolar air and blood would therefore be greater than 60 mm. The oxygen tension of alveolar air would probably also be greater than 100 mm. because of the increased depth of respiration, and this would increase further the head of pressure which drives oxygen through the alveolar membrane. Bøje[25] calculated that the greatest amount of oxygen that can be taken up in the lungs from ordinary air is 4,500 ml. per minute. Nielsen and Hansen,[120] in experiments in which trained athletes were subjected to exercise (on a stationary bicycle) to the limit of their capacities, found that the maximum possible oxygen absorption from room air was about 4,200 ml. per minute, which was not enough to meet the metabolic needs of the body. When oxygen was added to the inspired air, so as to raise the oxygen content to 45-47 per cent, the amount of oxygen absorbed increased by 500-800 ml. per minute, breathing was easier, and the subjects were able to continue the maximum effort longer than before. This indicates that it is possible to produce oxygen-lack in a normal individual by increasing the call for oxygen to a level higher than 4 liters per minute (approximately), but this can happen only in individuals in perfect physical condition. The elimination of carbon dioxide, however, remains adequate under all normal conditions, no matter how vigorous the exercise (until the circulation fails). Although the difference in tension of this gas is only 6 mm. (venous blood 46 mm., alveolar air 40 mm.) in the resting subject, the fact that CO_2 can traverse the alveolar membranes 20 to 30 times as readily as oxygen more than compensates for the smaller difference in tension, and CO_2 leaves the blood in the lungs even more readily than oxygen enters it. Even in disease, retention of CO_2 seldom if ever occurs without much greater shortage of oxygen.

*The work of Wearn and his co-workers is suggestive in this connection, for an increase in the area of the capillaries in which venous blood is exposed to alveolar air in the lungs would certainly work in this direction. There is as yet no evidence that this occurs during exercise.

We must not forget, however, that the blood is exposed to the alveolar air only for one second or less. This time is insufficient for complete equilibrium to be established between the oxygen tension of the alveolar air and that of the blood leaving the lungs. The oxygen tension of arterial blood is actually 5 to 25 mm. lower than that of the alveolar air; 90 mm. may be regarded as the average normal oxygen tension in arterial blood. This is the most vulnerable point in the entire process of respiration, for it is obvious that if the oxygen equilibrium between alveolar air and arterial blood is incomplete even when the rate of blood flow through the lungs is basal and the surfaces available for diffusion are normal in character and extent, there is likely to be a much greater disparity when cardiac output is increased, or the diffusion surface is reduced by disease. Dill,[47] Nielsen and Hansen,[120] and Krogh,[95] for various reasons, believe that this disparity is not due to a diffusion gradient (i.e., to inability of the membranes to pass sufficient amounts of oxygen into the blood) but rather to relative slowness of dissolved oxygen at reaching equilibrium with hemoglobin. An increase in the oxygen tension in the alveolar air would increase both the number of oxygen molecules and the rate at which they diffuse through the layers of blood in the pulmonary vessels and thus increase the oxygen saturation of the blood; the amount of the gas in physical solution (and therefore immediately available for the gas exchange of the tissues (page 699) would also be increased in proportion to the increased tension. Carbon dioxide diffuses so much more readily that the tension of this gas in the arterial blood is the same (40 mm.) as that in the alveolar air under all circumstances.

Secretion of Oxygen by the Lungs.—Under all ordinary circumstances the oxygen tension of the arterial blood is a little lower than that of the alveolar air, but as long as the oxygen tension in the inspired air is not reduced, enough oxygen can diffuse into the blood to supply all of the needs of the body for that gas. When the pressure of oxygen is reduced, however, the situation is different. There now are fewer molecules of oxygen in a given volume of air and they diffuse less rapidly. Is it possible for the alveolar epithelium under such circumstances to secrete oxygen into the blood so that the pressure of oxygen in the arterial blood is higher than that in the alveolar air?

For many years it was believed by some physiologists (notably J. S. Haldane) that this is the case, and a number of carefully made experiments seemed to support the belief. The practical importance is considerable, for when a person has been exposed for some time to a low tension of oxygen, as at a high altitude or in certain diseases which interfere with the oxygenation of the blood, he becomes acclimatized and can carry on activities which were impossible for him before compensation occurred. We will refer to this subject again in Chapter XLV. Haldane believed that the symptoms of oxygen-lack are relieved largely because of secretion of oxygen into the blood. However, Barcroft's party found during their sojourn at 14,200 feet above sea level that blood drawn directly from an artery was darker in color than at sea level and was only about 85 per cent saturated with oxygen instead of the 95 per cent which is normal at sea level; the oxygen tension of the blood was no higher than that of the alveolar air. Natives who had never lived elsewhere and whose ancestors had probably lived at that altitude for eight hundred years also showed arterial oxygen saturations of 85 per cent or less. Talbot and Dill[156] have made similar observations in six natives who resided and worked at an altitude of 17,500 feet; the oxygen saturation of arterial blood, collected by direct arterial puncture, ranged from 67.6 to 84.6 per cent and averaged 75 per cent; in ten temporary residents at the same altitude and at the same time of year the average arterial oxygen saturation was 76.2 per cent. "The absence of any difference between the arterial saturation in the temporary and the permanent residents suggests that permanent acclimatization is not associated with any significant change in this function of the blood" (Talbot and Dill).

The evidence at present is overwhelmingly against secretion of oxygen into the blood by the human lungs under any conditions. The uptake of oxygen in the lungs probably depends entirely upon diffusion of the gas from a point of higher pressure to one of lower, and the tension of oxygen can probably never become higher in the arterial blood than in the alveolar air; it is generally lower in the blood than in the alveolar air.[95]

Variations in the Rate of Diffusion of Oxygen.—The rate at which oxygen diffuses into the blood varies considerably among different individuals who presumably have normal pulmonary membranes. This is probably due partly to differences in the area of the capillaries in which blood is exposed to the alveolar air, partly to differences in the thickness of the membranes, and partly to differences in the effectiveness of the alveolar ventilation. Harrop[71] found that those men of Barcroft's expedition who had a diffusion constant for oxygen greater than 40 had practically no symptoms of mountain sickness when living at an altitude of 14,200 feet while those with lower coefficients suffered more or less severely. During a stay of several weeks at the higher altitude their diffusion coefficients did not change appreciably. There is at present no evidence that the oxygen diffusion constant increases when acclimatization takes place. It is true that Harrop also estimated the coefficients in five American engineers who had lived for two years or more at high altitudes and found them all above 40: the lowest was 41.5 and the highest was over 65, the latter in a man who had been a prominent runner during his college days. This may mean that some improvement takes place after long exposure to low tensions of oxygen, but it may also mean that only men who have high coefficients to begin with can stand the strain of continued activity at high altitudes.

It is certain, however, that the oxygen diffusion coefficient can be decreased considerably by diseases which reduce the effective surfaces in the lungs (such as emphysema, pneumonia, or collapse of the lung) or which cover the alveolar walls with a layer of fluid (as the result of inhalation of irritant gases such as chlorine, or possibly in cardiac disease).

Determination of the Tensions of the Gases in the Blood.—The tension in the arterial blood can be determined by exposing the blood at body temperature to mixtures containing different tensions of oxygen and CO_2 until one is found which neither gains nor loses gas during the exposure; this must have the same gas tensions as the blood. Direct determinations of the gas tensions in the circulating arterial blood were made by Krogh by means of a special microtonometer connected directly with an artery. A small bubble of air is exposed to the circulating blood, so that after a time actual equilibrium of gas tension becomes established between the bubble and the gases of the blood. This apparatus is shown in Figs. 245 and 246. It consists of a graduated tube of narrow bore surrounded by a water jacket. To the upper end of the graduated tube a small syringe is attached. The lower end of the graduated tube expands into a thistle-shaped bulb, closed below by a cork, through which is inserted a tube (inflow tube) ending near the top of the bulb in a fine opening and connected outside with an artery. An outflow tube is also connected with the thistle-shaped bulb.

At the beginning of the experiment the thistle-shaped bulb and the graduated tube are filled with physiological saline. By means of the syringe a small bubble of air is then introduced, so that it lies at the junction of the thistle-shaped bulb and the graduated tube. As the blood is allowed to enter through the inflow tube, it is ejected in a fine stream around the bubble of air, which moves about in the stream. The blood displaces the saline out of the bulb into the side tube. After the bubble has been subjected to the influence of the blood for some minutes, the gases in it come into perfect equilibrium with those in the blood.

The percentage of O_2 and CO_2 in the bubble will therefore correspond to the tension of these gases in the blood. The analysis is effected by drawing the bubble into the graduated tube by means of the syringe, measuring its capacity, transferring it into a bulb containing KOH, which absorbs the CO_2, then taking it back into the capillary tube and again measuring. The shrinkage obviously corresponds to the amount of CO_2. The bubble is then transferred into potassium pyrogallate solution, where the O_2 is absorbed.

The same procedure can be used to determine the tensions of the gases in blood drawn directly from an artery of man: a small bubble of air is introduced into the blood in a tonometer like Krogh's and after equilibrium has been reached the gas tensions of the air in the bubble are determined by analysis.

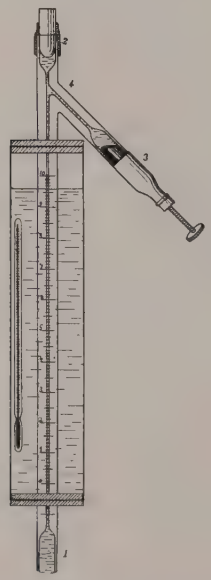


Fig. 245.

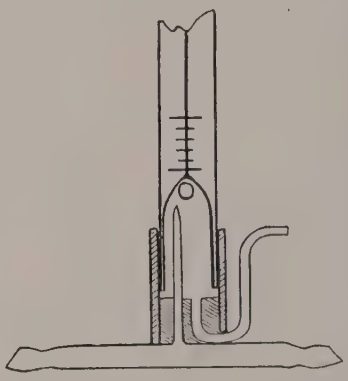


Fig. 246.

Fig. 245.—The gas analysis pipette for the microtonometer shown in Fig. 246. For description see text. (From A. Krogh: Skand. Arch. f. Physiol. 20: 259, 1907-08.)

Fig. 246.—Microtonometer, to be inserted into a blood vessel. The small circle represents the bubble of air. For further description see text. (From A. Krogh: Skand. Arch. f. Physiol. 23: 193, 1909-10.)

The tensions of the gases in the mixed venous blood can be determined directly in animals by withdrawing blood from the right ventricle, but this procedure obviously is not to be recommended for studies in man. Christiansen, Douglas, and Haldane[34] introduced a method which depends upon ascertaining the gas mixture which is in tension equilibrium with the venous blood, but in this case the lungs are used as the equilibrating vessel. The procedure in determining the CO_2 tension of the venous blood is as follows. Three Douglas bags provided with valves are used: *A* containing 7.5 per cent CO_2; *B*, 7 per cent, and *C*, 6.5 per cent. The subject expires as deeply as possible through a respiratory valve and then fills the lungs with air from bag *A* (by connecting the bag with the inspiration valve and taking three deep breaths). He then expires about half way through a piece of hose pipe, and a sample of air is collected in a Haldane gas sampling tube or all-glass syringe. The remaining half of the air is retained in the lungs for five or six seconds when it also is expired through the hose pipe, and another sample is collected. The two samples of alveolar air are analyzed for CO_2. Exactly the same procedure is repeated with the air in bags *B* and *C*. The alveolar venous tension of CO_2 will then correspond to the percentage in the bag with which no change occurred in the two alveolar samples. Thus,

supposing with bag *A* that Sample 1 contained 7.4 per cent CO_2 and Sample 2, 7.2 per cent, and with bag *B*, that both Samples 1 and 2 contained 7 per cent, and with bag *C*, that Sample 1 contained 6.6 per cent and Sample 2, 6.8 per cent; then clearly equilibrium was established at 7 per cent CO_2 which is, therefore, the venous tension.

In Pearce's method[125] the person first of all inspires from a gas meter containing a gaseous mixture with about 10 per cent of CO_2. Immediately after filling the lungs, he makes a rapid forced expiration into a tube provided with a valve having four openings. This valve is turned through a complete circuit during the expiration, so that four fractions of the expired air can be collected in rubber bags connected with side tubes opening opposite each of the four openings in the valve. The first fraction will contain a little less than 10 per cent CO_2, the second distinctly less, while the third and fourth should contain the same percentage, indicating that equilibrium between the CO_2 of the alveolar air and the blood has been attained. This figure gives us the tension of CO_2 in the venous blood of the lungs. In Henderson's method the rebreathing is performed into gas receivers containing 6 per cent CO_2.

The tension of O_2 in the venous blood of the lungs (mixed venous blood) may be determined by the application of similar principles. After a deep expiration nitrogen is inspired for 3-5 breaths (10-20 sec.) from a rubber bag provided with valves, and a sample of alveolar air is immediately taken. The percentage of O_2 in this alveolar air will be found to be the same whether it be taken after 3 or 5 breaths, showing that an equilibrium with the tension of this gas in the blood must have been reached. If taken earlier, the O_2 will be too high, and if taken later it will be too low, because the blood will have circulated twice round the body (Barcroft). This oxygen percentage is somewhat lower than that corresponding to the tension of oxygen in the venous blood of the lungs, on account of the fact that the tension of CO_2 in the alveolar air, under the conditions of the experiment, corresponds to that of the arterial blood.

THE PART PLAYED BY CHEMICAL CHANGES IN THE BLOOD IN THE LUNGS

In addition to the factors which we have just been considering, the uptake of oxygen by the venous blood is aided to a considerable extent by the removal of CO_2 from it. On the other hand, the removal of CO_2 is aided to an even greater extent by the uptake of oxygen. This brings us to a consideration of the physicochemical changes in the blood associated with the transport of the respiratory gases—a question which will be taken up in the next chapter. At this point it will suffice to summarize briefly the changes which assist in bringing about the gas exchange in the lungs.

The oxygen and CO_2 carried by the blood (with the exception of the 0.3 ml. of O_2 and 3.0 ml. of CO_2 which are simply dissolved in each 100 ml. of the plasma) are held in chemical combinations which represent the equilibria of a series of reversible physicochemical reactions at the tensions of oxygen and CO_2 existing in the plasma. As soon as the tensions of the gases are altered, all of these chemical combinations are altered correspondingly. In the lungs the venous blood (oxygen tension 40 mm., CO_2 tension 46 mm.) is exposed to an oxygen tension of 100 mm. and a CO_2 tension of 40 mm. Oxygen promptly diffuses into the plasma and CO_2 out of it. The added oxygen is taken up by the hemoglobin, which is thus transformed from the reduced to the oxygenated form. Oxyhemoglobin is a stronger acid than reduced: it requires alkali, which it takes from other anions (Cl^-, HCO_3^-) present in the erythrocytes. As a result of this appropriation of a number of cations by oxyhemoglobin a corresponding number of chlorine ions diffuse out into the plasma and bicarbonate ions diffuse into the erythrocytes in exchange. This bicarbonate is promptly decomposed to CO_2 and water, the reaction being greatly accelerated by an enzyme (carbonic

anhydrase) present within the erythrocytes, and the CO_2 diffuses out into the plasma and thence into the alveolar air. The oxygenation of hemoglobin also leads to the splitting off of CO_2 from amino groups with which it was held in combination before the hemoglobin took up oxygen but which can no longer hold it when the molecule becomes more acid as a result of oxygenation; this CO_2 also diffuses out into the plasma and thence into the alveoli. Meanwhile as soon as the CO_2 dissolved in the plasma can diffuse out of the blood into the alveolar air the CO_2 tension of the plasma falls, the equilibria of the reactions concerned in binding CO_2 are disturbed, and CO_2 is liberated from chemical combination for that reason as well as the ones mentioned above. The loss of CO_2 from the blood makes it more alkaline and this enables hemoglobin to combine with more oxygen than it would if the reaction of the blood remained the same. Thus the uptake of oxygen turns CO_2 out of the blood and the loss of CO_2 enables the blood to take up more oxygen. As we shall see, this relation is exactly reversed in the tissues.

CHAPTER XLIII

THE TRANSPORT OF THE RESPIRATORY GASES BY THE BLOOD

We have now completed our survey of the various mechanisms involved in *external respiration;* i.e., in the exchange of gases between the blood and the external environment (air) in the lungs. We have seen how the respiratory movements are adjusted to the needs of the body for the uptake of oxygen and the removal of CO_2. We have considered the factors which cooperate to change the character of the blood from venous to arterial in its passage through the lungs, and in so doing have encountered some examples of the remarkable way in which the blood performs its share of the respiratory process. It is necessary now to consider the respiratory function of the blood, for this is the link which connects the gas exchange in the lungs with that in the tissues; tissue respiration will be taken up in Chapter XLVII.

Let us consider first the amounts of the gases in the blood. These are best determined by the method of Van Slyke and Neill.[143] The apparatus used is shown in Fig. 247.

At the start of an analysis the analyzer is filled with mercury. A measured quantity of blood is then drawn into it together with a gas-free reagent which combines with the blood so as to liberate its gases from chemical combination. The mixture is then subjected to a torricellian vacuum by lowering the mercury leveling bulb. After shaking for a few minutes the gases will be completely removed from the blood and will exert a pressure upon the surface of the mercury. This pressure is measured by determining the height of the mercury column in the vertical tube at the left that is required to bring the volume of the gases to a constant volume, e.g., 2 ml. Strong alkali (NaOH) is then introduced to absorb CO_2, and, after mixing, the gas pressure is again read; this reading is lower than the first, and the difference represents the CO_2. To determine the oxygen, sodium hyposulfite solution is introduced to absorb it and the oxygen pressure is determined by the extent to which absorption of the gas has reduced the pressure.

The reagent for determination of CO_2 alone contains lactic acid to decompose the alkali compounds of the blood and caprylic alcohol to prevent foaming. For determination of oxygen alone a mixture of potassium ferricyanide (which liberates oxygen from hemoglobin, while changing the latter to methemoglobin), saponin (which causes hemolysis—a necessary step since ferricyanide cannot enter the red cells) and caprylic alcohol is used; CO_2 is absorbed by NaOH before the first reading is made. To determine both CO_2 and oxygen in the same sample of blood a mixture of lactic acid, sodium ferricyanide, saponin, and caprylic alcohol is used; the CO_2 is first measured by absorption with NaOH and the oxygen is then estimated by absorption with sodium hyposulfite.

This manometric method permits greater precision than the original volumetric procedure of Van Slyke, although the apparatus used in the latter is simpler and the method is sufficiently accurate for most clinical work. For details the reader is referred to Peters and Van Slyke (vol. 2).

The average amounts of oxygen and CO_2 in the blood of healthy young adults at rest are approximately (in ml. per 100):

	Oxygen	CO_2
Mixed venous blood	15	52
Arterial blood	20	48

The amounts of these gases that can be dissolved (without chemical reaction) by blood at 38° C. under the tensions existing in the alveolar air are about 0.3 ml. of oxygen per 100 (at a tension of 100 mm. Hg) and about 3.0 ml. of CO_2 per 100 (at a tension of 40 mm. Hg). Now the amount of oxygen con-

sumed by an individual at rest is seldom if ever less than 200 ml. per minute. To supply this minimal quantity of oxygen to the tissues the cardiac output need be only 4 liters per minute when each 100 ml. of blood gives up 5 ml. of oxygen, as it normally does. But if the body had to depend upon the oxygen carried in simple solution in the blood, and even if the entire 0.3 ml. carried by each 100 ml. were taken out of it (which could scarcely occur) the heart would have to pump nearly 70 liters of blood per minute to meet the needs of the body at rest—an impossible task. During exercise the oxygen consumption often is greater than 3 liters per minute; to meet this demand from oxygen carried in solution in the blood would require a cardiac output of more than 1000 liters per minute. The importance of some agent for carrying oxygen in chemical combination is of course evident.

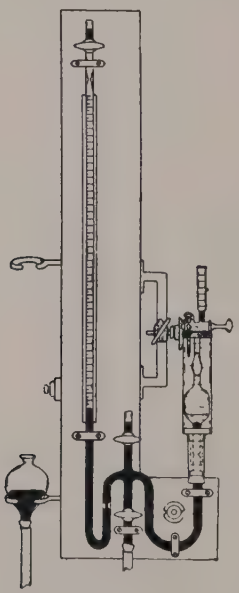


Fig. 247.—Manometric apparatus for blood-gas analysis. (From Van Slyke and Neill: J. Biol. Chem. 61: 523, 1924.)

It must not be supposed that the gases carried in physical solution are unimportant simply because their quantities are relatively small. On the contrary it is only the gases in solution that can take a direct part in the gas exchange; the larger amounts that are carried in chemical combinations are physiologically inactive until the gas molecules are released from chemical combination. But we have just seen that the amounts of oxygen carried in solution are entirely insufficient for the needs of the body, even at rest. The basic fact of respiration beyond the lungs is thus brought to our attention. It is this: *The volume of each of the respiratory gases carried in chemical combination in the blood varies directly with the tension of the same gas in the plasma and inversely with the tension of the other gas.*

The general scheme is as follows: If we start with the mixed venous blood of a resting individual we find a tension of oxygen of 40 mm. and a tension of CO_2 of 46 mm. After the blood leaves the tissue capillaries and until it arrives in the lungs there is no opportunity for gas to enter or leave it and the reversible chemical reactions in which the gases are involved come to an equilibrium at those tensions. In the lungs the blood is exposed over an enormously large surface and in a very thin layer to a higher tension of oxygen (100 mm.) and a lower tension of CO_2 (40 mm.). Oxygen immediately diffuses into the plasma and CO_2 out of it. This upsets the equilibria. More oxygen can be taken up in chemical combination at the higher tension and this promptly occurs; less CO_2 can be bound chemically at the lower tension and its combinations are accordingly broken down to liberate CO_2 molecules which diffuse out of the blood and into the alveolar air. At the same time, as we have already seen (page 625), the taking up of oxygen automatically reduces the ability of the blood to carry CO_2 and most of the elimination of CO_2 by the lungs is due to that fact. Loss of CO_2 also makes the blood less acid and enables it to combine with more oxygen.

The arterial blood as it leaves the lungs has gained 5 ml. of oxygen and has lost 4 ml. of CO_2 per 100 (page 627). The tension of oxygen is about 90 mm. and that of CO_2 40 mm. There can be no further change until the blood reaches the capillaries, and the chemical reactions involving the gases therefore come to an equilibrium at those tensions. In the tissues the processes which we have just described in the lungs are reversed. The tension of oxygen is low (15-27 mm. in the subcutaneous tissues of man at rest—Seevers[146]) and oxygen diffuses out of the plasma; this causes a breakdown of the chemical combination in which oxygen is held and more of the gas escapes into the plasma and thence into the tissues. The tension of CO_2 is high—over 46 mm.—and this gas diffuses into the blood which therefore becomes more acid. This leads to a reapportionment of alkali in the blood, one result of which is to decrease the amount of oxygen which can be held in chemical combination at that tension of oxygen; consequently more oxygen molecules are liberated into the plasma and thence into the tissues. After losing oxygen the blood is able to carry more CO_2 in chemical combination and thus a new equilibrium is attained—that of mixed venous blood, with which we started. The blood has lost 5 ml. of oxygen and gained 4 ml. of CO_2 per 100.

Such is the situation when the body is at rest. During violent exercise the amount of oxygen taken out of each 100 ml. of blood may increase from 4 ml. to 15 ml. or more, so that the blood which reaches the lungs may contain as little as 4 ml. of oxygen per 100. Yet it still emerges from the lungs containing 20 ml. of oxygen per 100. The adequacy of this mechanism to meet greatly changing conditions is thus quite evident.

The substance responsible for practically all of the transport of the respiratory gases is hemoglobin. Its properties and the reactions through which its functions are carried out will now be considered briefly.

THE PROPERTIES OF HEMOGLOBIN

A complete discussion of the chemical composition and known properties of hemoglobin is beyond the scope of this book. The reader is referred to Barcroft[13, 14] and Peters and Van Slyke[126] for such information. For our purposes it is sufficient to note the following essential facts.

In man and other mammals hemoglobin normally exists only inside the erythrocytes; consequently any molecule or ion that enters or leaves a chemical combination with hemoglobin must pass through the walls of these cells which are freely permeable to oxygen and CO_2 and to anions such as Cl^- and HCO_3^-, but not to cations such as Na^+ and K^+. Hemoglobin is a protein which has a molecular weight of about 68,000 and contains iron in the ferrous state, four atoms to each molecule of hemoglobin. It possesses a number of groups which are capable of combining with alkali and acid, and at the hydrion concentration encountered inside the erythrocyte (about pH 7.25) it acts as a weak polyvalent acid (a buffer) which has combined with alkali (mainly potassium) to form soluble salts. Hemoglobin comprises 32 per cent of the contents of the erythro-

cyte, the remainder consisting of water (65 per cent) and inorganic salts (3 per cent). The ability of hemoglobin to combine reversibly with oxygen depends entirely on the iron of the molecule. One atom of ferrous iron (Fe^{++}) combines with one molecule of oxygen (O_2). This is also true of the combination with carbon monoxide. When the hemoglobin iron is oxidized to the ferric form (Fe^{+++}) it loses its power to combine reversibly with O_2 or CO; this is methemoglobin, which cannot carry oxygen. The function of hemoglobin as a carrier of CO_2 depends partly upon the formation of unstable carbamino or carbamate compounds ($CO_2 + RNH_2 \rightleftharpoons RNHCOOH$), but in much larger part upon the buffer property, which in this case means that hemoglobin can give up alkali when CO_2 enters, thus forming bicarbonate, and take up the alkali again when the bicarbonate is broken down. About 20 per cent of the CO_2 that is given off in the lungs is carried in the blood in carbamino combination with hemoglobin while about 70 per cent is carried as bicarbonate; the alkali for the latter is obtained from the buffer groups of hemoglobin. The formation of bicarbonate takes place almost entirely within the erythrocytes because the first step in the process is hydration of CO_2 molecules to carbonic acid ($CO_2 + H_2O \rightleftharpoons H_2CO_3$); this reaction occurs much too slowly for physiological purposes unless it is catalyzed by the enzyme *carbonic anhydrase,* which is found only inside the erythrocytes. When carbonic acid is formed inside the erythrocyte, bicarbonate ions are at once split off and some of them (about one third) remain inside the erythrocytes, but the remainder diffuse out into the plasma. For this to occur an equal number of chlorine ions must diffuse into the cells from the plasma in exchange for the bicarbonate ions (Roughton).

The quantity of hemoglobin in the blood varies greatly with age. (See Peters and Van Slyke,[126] p. 544.) In healthy adult males between 16 and 60 years of age, it is about 15.6 grams per 100 ml. of blood. One gram of hemoglobin can combine (at full saturation) with about 1.34 ml. of oxygen. Consequently 100 ml. of blood from a normal adult male, when saturated with oxygen, should contain 20.9 ml. of oxygen in chemical combination. Since the oxygen content of blood can be determined very accurately, the oxygen-combining power is the easiest way to determine accurately the hemoglobin content of blood, and for adult males the standard is that just given, i.e., 20.9 ml. O_2 capacity per 100 ml. blood. In females the hemoglobin content is normally about 90 per cent of that of males and the corresponding standard is about 19 ml. O_2 capacity per 100 ml.*

THE COMBINATION OF HEMOGLOBIN WITH OXYGEN

"The physiological value of hemoglobin as an oxygen carrier lies in the fact that its affinity for oxygen is so nicely balanced that in the lungs hemoglobin becomes 95 to 96 per cent oxygenated, while in the tissues and capillaries it can give up as much of the gas as is demanded. If the affinity were much less, complete oxygenation in the lungs could not be approached: if it were greater, the tissues would have difficulty in removing from the blood the oxygen they need. Because the affinity is adjusted as it is, both oxyhemoglobin and

*These figures must not be confused with those for the oxygen content of arterial blood, which is normally 95 to 96 per cent saturated with oxygen; arterial blood of males should contain about 20 ml. of O_2 per 100 ml., that of females about 18 ml. per 100. It is a coincidence that atmospheric air at sea level contains 20.9 ml. of oxygen per 100 ml. of air—the same figure as that for the oxygen capacity of the blood of men.

reduced hemoglobin exist in all parts of the circulation, but in greatly varied proportions'' (Peters and Van Slyke[126]).

The ability of hemoglobin to function as an efficient carrier of oxygen depends upon the fact that the amount of oxygen held by it in chemical combination varies directly with the tension of oxygen and inversely with the tension of CO_2. As we have seen (page 629) venous blood takes up oxygen and loses CO_2 in the lungs, while in the tissues the process is reversed. Hemoglobin acts as a storehouse for oxygen, delivering to the tissues as much of the gas as they require. The need is expressed in the tensions of oxygen and CO_2 in the tissues: the more active the metabolism, the lower the tension of oxygen and the higher the tension of CO_2 to which the blood is exposed in the capillaries.

The combination of oxygen with hemoglobin is a reversible chemical reaction: $Hb + O_2 \rightleftharpoons HbO_2$. The relative amounts of reduced (Hb) and oxygenated (HbO_2) hemoglobin depend entirely upon the pressure (tension) of O_2 provided that everything else is unchanged. But increased acidity diminishes the amount of oxygen with which hemoglobin can combine at a given oxygen tension, and decreased acidity has the opposite effect. The tissues contain large amounts of

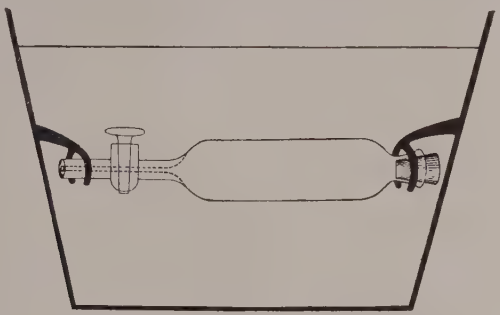


Fig. 248.—Barcroft's tonometer for determining the curve of absorption of oxygen by hemoglobin. (From Starling's Physiology.)

CO_2. This gas diffuses very readily into the blood and expels oxygen from it both directly, by combining with hemoglobin to form carbamates which reduce the oxygen-binding power of hemoglobin, and indirectly by combining with water to form carbonate, from which hydrogen ions are dissociated, thus increasing the acidity of the blood. Hence oxygen leaves the blood in the tissue capillaries both because the oxygen tension outside the capillaries is lower than that inside and because the ability of hemoglobin to combine with oxygen at the existing tension is reduced by diffusion of CO_2 and fixed acid (if present) into the blood. In the lungs both factors cooperate to oxygenate the hemoglobin: the oxygen tension is high and the CO_2 tension is low, so that acid diffuses out of the blood as oxygen diffuses into it.

These facts are conveniently demonstrated by plotting curves to show the extent to which hemoglobin is saturated with oxygen at different tensions of the gas. These are known as *dissociation curves.* To obtain the data necessary to construct them one must first expose small amounts (e.g., 3 ml.) of blood or hemoglobin solution to relatively large amounts (about 400 ml.) of gas mixtures in which the oxygen tension is known. This is done in glass vessels, known as tonometers (Fig. 248), which are slowly rotated in a water-bath at a known temperature until the blood, which is spread out in a thin film on the walls of the tonometers,

comes to equilibrium with the gas mixture. The tension of oxygen in the blood is now equal to that in the gas mixture, and the latter can be calculated from the percentage of oxygen which it contains. The oxygen content of each of the blood samples is then determined by a suitable method such as that of Van Slyke (p. 627). One now knows the amount of oxygen taken up by 1 ml. (or 100 ml.) of that particular blood or hemoglobin at each of the oxygen tensions that were investigated.

It must be realized that the amount of oxygen taken up by a sample of blood at a given tension of oxygen varies with the amount of hemoglobin present. To correct for this and to permit comparison between different samples of blood, it is necessary to know the quantity of oxygen which the blood can take up when fully saturated. This is determined by exposing the blood to an excess of room air (O_2 tension 159 mm. Hg at sea level) until no more oxygen is taken up. The oxygen content of this sample represents full saturation (HbO_2 = 100 per cent; Hb = O). At lower oxygen tensions there will be varying mixtures of reduced hemoglobin and oxyhemoglobin and the percentage saturation, $\frac{\text{oxygen content}}{\text{oxygen capacity}} \times 100$ is the figure used in plotting dissociation curves.

The effect of CO_2 on the dissociation curves for oxygen is studied by adding CO_2 in varying tensions to the gas mixtures in the tonometers. The effects of temperature, concentration of hemoglobin, and electrolyte content have also been investigated in a similar way.

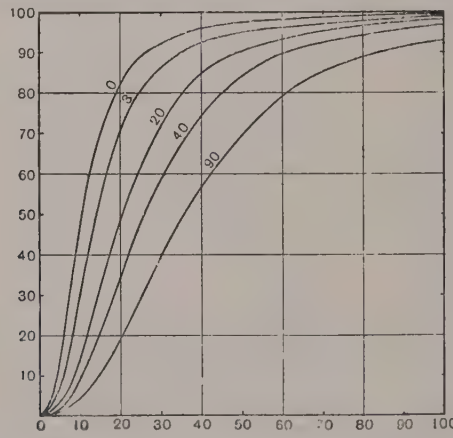


Fig. 249.—Dissociation curves of human blood exposed to 0, 3, 20, 40, and 90 mm. CO_2. Ordinate, percentage saturation. Abscissae, oxygen pressure. (From Joseph Barcroft.)

Dissociation curves obtained in this way are shown in Fig. 249. The tensions of oxygen are plotted as abscissae, the percentage saturation of the blood with oxygen as ordinates. All of these curves were obtained with the same sample of human blood at 38° C. The important points are these:

The oxygen dissociation curves of blood are characteristically S-shaped.* They are shifted to the right as the CO_2 tension is increased, which means that

*Pure solutions of hemoglobin at room temperature, if weak (1:500) and free from such electrolytes as are found in blood plasma, give a hyperbolic dissociation curve; i.e., the curve rises steeply in a straight line, then flattens out horizontally. Stronger solutions give an S-shaped curve and it is probable that the typical S-shaped curve of blood is to some extent due to the high concentration of hemoglobin. Either raising the temperature or adding electrolytes introduces a slight S-shape into the dissociation curve of a weak hemoglobin solution, and these factors also help to give the curve of whole blood its characteristic appearance, but they are relatively unimportant. For our purposes the behavior of whole blood at 38° C. is of greatest importance, and the only variables that need be considered are the tensions of oxygen and the tensions of CO_2 or the hydrion concentration; the hemoglobin concentrations and electrolyte content are constant. Temperature is probably higher in active tissues than elsewhere, and this shifts the curve to the right; i.e., it decreases the affinity of hemoglobin for oxygen at the existing tensions of oxygen and CO_2; this undoubtedly helps to unload oxygen in active tissues.

the addition of CO_2 (or increased acidity in general, for an equal change in pH produced by any other acid has the same effect) reduces the ability of hemoglobin to hold oxygen, and a loss of CO_2 (or greater alkalinity) enables hemoglobin to combine with more oxygen, at the same oxygen tension. Arterial blood (O_2 = 90 mm., CO_2 = 40 mm.) is about 95 per cent saturated with oxygen; i.e., it contains about 20 ml. of O_2 per 100 ml. Under resting conditions mixed venous blood (O_2 = 40 mm., CO_2 = 46 mm.) is about 72 per cent saturated with oxygen, i.e., it contains about 15 ml. of O_2 per 100; in the tissues the blood has lost 5 ml. of O_2 per 100. The curve obtained at 40 mm. tension of CO_2 is the one which most closely approximates ordinary physiological conditions; the steepest slope is seen to occur when the oxygen tension falls below 40 mm., which means that as the tissues need more oxygen the hemoglobin parts more and more readily with it and the blood emerges more and more nearly reduced. At a tissue oxygen tension of 30 mm., for instance, this blood would be only 55 per cent saturated; i.e., it would have yielded more than 9 ml. of O_2 per 100. At a tissue oxygen tension of 10 mm. it would be about 8 per cent saturated, i.e., it would emerge with less than 2 ml. of oxygen per 100 and would have given up more than 18 ml. per 100. Since a fall in tissue oxygen tension, if due to increased activity of the tissue, would also be accompanied by an increase in CO_2 tension and in temperature, the blood will yield oxygen at a higher tissue oxygen tension than it would if the CO_2 tension remained at 40 mm. and the temperature at 38° C.

TABLE XXII

EFFECT OF OXYGEN AND CARBON DIOXIDE TENSIONS ON OXYGENATION OF HEMOGLOBIN IN THE HUMAN BLOOD

O_2 TENSION	O_2 PHYSICALLY DISSOLVED	PROPORTION OF HEMOGLOBIN COMBINED WITH OXYGEN AT FOLLOWING CO_2 TENSIONS			
		CO_2 = 3 MM.	CO_2 = 20 MM.	CO_2 = 40 MM.	CO_2 = 80 MM.
mm.	vols. per cent	per cent	per cent	per cent	per cent
0	0.00	0	0	0	0
5	0.012	13.5	6.8	5.5	3.0
10	0.025	38.0	19.5	15.0	8.0
20	0.050	77.6	50.0	39.0	26.0
30	0.075	92.0	72.2	60.6	49.8
40	0.100	96.7	87.0	76.0	63.5
50	0.125	98.5	93.3	85.5	76.9
60	0.150	100.0	96.3	90.5	85.0
70	0.175	100.0	98.0	94.0	90.3
80	0.200	100.0	99+	96.0	93.7
90	0.225	100.0	100.0	97.5	95.7
100	0.25	100.0	100.0	98.6	97.1
760	1.90	100.0	100.0	100.0	100.0

(From Peters and Van Slyke: Quantitative Clinical Chemistry, Vol. I, Baltimore, 1931, Williams and Wilkins Co.)

Table XXII gives data which illustrate these points, and Fig. 250 is a chart in which the relation of the oxygen saturation of blood to the oxygen tension and acidity of the blood is shown under two sets of conditions—rest, and work strenuous enough to increase the oxygen consumption to seven times the resting value. The blood of this subject (Fig. 250) at rest was giving up 4.6 ml. of oxygen per 100 ml. in his tissues (arterial blood 96 per cent saturated with oxygen, venous blood 74 per cent saturated; oxygen capacity assumed to be 21 ml. per 100). At work his blood gave up just twice as much oxygen (9.2 ml. per 100), changing from 94 per cent (arterial) to 50 per cent (venous) saturation. The arterial oxygen tension was 78 mm. at rest, 73 mm. during exer-

cise. The venous oxygen tension was 41 mm. in the resting state, 32 mm. at work. If the acidity of the blood had not been increased in the tissues when work was done (i.e., if the pH of the venous blood had remained at 7.35, its arterial level) the blood would have emerged from the tissues 56 per cent oxygenated at 32 mm. oxygen tension instead of the 50 per cent actually observed, and each 100 ml. of blood would have yielded only 8 ml. of oxygen instead of 9.2 ml. In other words, lowering the pH of the plasma from 7.35 to 7.28 by diffusion of CO_2 (and possibly acids such as lactic) into the capillaries accounted for the liberation of about 13 per cent of the total amount of oxygen given up to the tissues, the remaining 87 per cent being set free because of the lower oxygen tension alone. Greater acidity would have a greater effect, and it would be

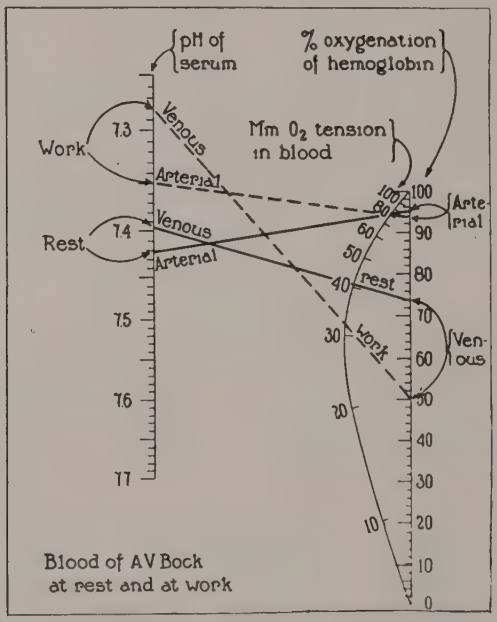


Fig. 250.—Line chart showing amounts of oxygen bound by hemoglobin of the blood of subject shown in Table XXII, at rest (unbroken lines) and while doing work sufficient to increase oxygen intake seven fold (broken lines). A straight line drawn through selected points on any two of the three scales cuts the third scale at the point corresponding with the other two. (From Peters and Van Slyke: Quantitative Clinical Chemistry, Vol. I, Baltimore, 1931, Williams and Wilkins Co.)

most marked when the tissues are most in need of oxygen, as at high altitudes, or during violent exertion, or in diseases in which anoxia occurs. In such circumstances lactic acid, in addition to CO_2, is likely to enter the blood from the tissues and the acidity of the blood would thereby be increased to an unusual degree; blood pH may fall below 7.0 if muscular exercise is carried to the point of collapse, as in a long run culminating in a sprint (Laug[98]).

From these examples we see why it is that the characteristic S-shaped dissociation curve of hemoglobin gives an excellent picture of the ability of this substance to yield oxygen in proportion to the needs of the tissues, for the steepest part of the curve lies just below the oxygen tensions usually found in

the tissues at rest and the CO_2 produced by the tissues helps to a slight but important extent in releasing oxygen from its combination with hemoglobin. We can also see why increased alkalinity of the blood will cause the hemoglobin to combine with more oxygen and to yield it only at a lower oxygen tension.

One important point has not yet been mentioned, namely, the significance of the flat top of the curve. If we follow the dissociation curve at 40 mm. CO_2 tension in Fig. 249 we see that an increase of oxygen tension from 0 to 30 mm. leads to 60 per cent saturation of the blood with oxygen; a further rise to 60 mm. oxygen tension causes the blood to be almost 90 per cent saturated; a further rise to 100 mm. oxygen tension only makes the saturation 96 per cent. The importance of this is quite evident if we consider what happens when the body is exposed to decreased oxygen tensions, as at high altitudes, for even though the oxygen tension falls to 60 mm. (corresponding to an altitude of 14,000 feet) the blood is still nearly 90 per cent saturated with oxygen. At oxygen tensions lower than this the saturation of hemoglobin begins to fall sharply, and it is largely for this reason that permanent residence above 14,000 feet is unpleasant or hazardous for most people.

The velocity of the reaction $Hb + O_2 \rightleftharpoons HbO_2$ has not been taken into consideration up to this point, for in obtaining data for dissociation curves one allows sufficient time for equilibrium to be attained. It is probable that a given molecule of hemoglobin traverses the pulmonary circulation in not more than one second, and the time spent in the tissue capillaries is about the same. Unless the reactions which we have just been describing can take place in the body within one second the dissociation curves have little practical importance. This feature of the problem has been attacked by Hartridge and Roughton[72] who observed with a special spectroscope the rate at which the absorption bands of reduced hemoglobin change to those of oxyhemoglobin when reduced blood is mixed with oxygenated Ringer's solution and made to flow through an observation chamber. They found that under their experimental conditions reduced hemoglobin becomes oxyhemoglobin in less than 0.01 second. Oxyhemoglobin was also found to give up its oxygen with extreme rapidity, and the reaction is accelerated by increased temperature or increased CO_2 tension. The one second allotted a molecule of hemoglobin to take up oxygen in the lungs and to yield it in the tissues is much more time than is required for the reaction $Hb + O_2 \rightleftharpoons HbO_2$ to proceed to completion in either direction. But we must remember that the gas diffuses through the capillary walls and through the membrane of the erythrocytes, as well as through the blood plasma, and this takes a certain amount of time. We have already seen (page 622) that the blood leaving the lungs has not quite come to equilibrium with the oxygen tension of the alveolar air (90 mm. or less in blood, 100 mm. in alveolar air). This is probably because of incomplete exposure of the hemoglobin molecules to the oxygen; equilibrium of the tension of this gas between the plasma in contact with the alveolar surfaces and the interior of the erythrocytes apparently is not reached during the time available for the process, so that the equilibrium actually struck is at a tension of oxygen lower than that in the alveolar air.

THE TRANSPORT OF CARBON DIOXIDE

The total amount of CO_2 that can be extracted from the arterial blood of normal persons averages about 48 ml. per 100, the normal range being from 41 to 55 ml. At rest the amount in venous blood is about 4 ml. more than this,

i.e., about 52 ml. per 100; during muscular activity the venous blood may contain as much as 65 ml. of CO_2 per 100, or even more, but in the passage through the lungs practically all of the excess CO_2 is lost and the arterial blood emerges with only a little more CO_2 than it holds under resting conditions. The CO_2 tension of arterial blood is about 40 mm. It is the same as that of the alveolar air, because CO_2 diffuses so rapidly that the blood and the alveolar air normally always come to complete equilibrium with respect to CO_2 tension. For the same reason the tension of CO_2 in the venous blood is probably equal to that in the tissues; at rest this tension is about 46 mm., while during exercise it may rise to 60 mm. The amount of CO_2 that can be dissolved by blood exposed to a tension of 40 mm. of CO_2 at body temperature is only about 3 ml. per 100. Consequently 45 of the 48 ml. of CO_2 yielded by 100 ml. of arterial blood must be in chemical combination. About one-fifth of it (about 10 ml.) is combined directly with amino groups of hemoglobin (carbamino-bound or carbamate CO_2, RNHCOOH). The remainder is carried as bicarbonate ($BHCO_3$), and practically all of it is formed inside the erythrocytes through the action of the enzyme carbonic anhydrase. After bicarbonate ions are formed inside the erythrocyte most of them (two-thirds or more) diffuse out of the cells into the plasma and an equal number of chlorine ions diffuse into the cells in exchange. Thus as the bicarbonate content of the plasma increases, the chloride content decreases, and conversely. The base (B) does not pass from cells to plasma, for the wall of the erythrocyte is impermeable to cations; anions can traverse it and the interchange of Cl^- with HCO_3^- accounts for the changes in bicarbonate content of the plasma.

The amount of CO_2 that can be carried by a given sample of blood varies directly with the CO_2 tension and inversely with the oxygen tension. This can be shown by constructing CO_2 dissociation curves.

To obtain the necessary data samples of blood are exposed at 38° C. in tonometers to varying tensions of CO_2 until equilibrium is attained. The CO_2 contents of the blood samples are determined by the method of Van Slyke (page 627). The CO_2 tensions of the gas mixtures are plotted as abscissae, the amounts of CO_2 (in ml.) liberated from 100 ml. of blood as ordinates. To study the effect of oxygenation, mixtures of hydrogen and CO_2 are used to obtain one set of data and mixtures of hydrogen (or nitrogen), oxygen, and CO_2 for another; the tension of oxygen in the latter series should be sufficient to saturate the hemoglobin with oxygen (i.e., 100 mm.).

Typical CO_2 dissociation curves are shown in Fig. 251. Here a curve for the CO_2 taken up by a sodium bicarbonate solution of strength comparable with the bicarbonate of normal blood (0.02 molar) and a curve for the amount of CO_2 taken up in physical solution are also shown.

The most important feature of the curves for blood is that the amount of CO_2 taken up by blood increases as the CO_2 tension is increased, and the slope is much steeper than the curve representing CO_2 dissolved in the plasma. Clearly the blood has a reserve capacity for combining chemically with more CO_2 than it is usually called upon to take up in the body. When the CO_2 tension is reduced, the blood gives off CO_2, and at zero CO_2 tension (as in a vacuum) blood readily gives up all of its CO_2. The bicarbonate solution, on the other hand, combines with all the CO_2 with which it can enter into chemical combination at a tension considerably below 10 mm.; above this tension all of its alkali exists as bicarbonate ($BHCO_3$) and there is no carbonate (B_2CO_3); at zero CO_2 tension

half of the $BHCO_3$ is decomposed to yield water and CO_2, but the remainder is present as B_2CO_3 and no more CO_2 can be obtained from the solution unless acid is added to decompose the carbonate. At tensions of CO_2 above 10 mm. the bicarbonate solution takes up more CO_2 in solution but does not combine with any more, so that the curve is parallel to that representing CO_2 in physical solution. The decomposition of a bicarbonate solution to liberate CO_2 according to the reaction: $2\,BHCO_3 \rightarrow B_2CO_3 + CO_2 + H_2O$ takes place quite slowly even in vacuo, several minutes being required for the reaction to be completed, and even then only half of the CO_2 is liberated. Blood, on the other hand, liberates all of its CO_2 in vacuo. This is because the hemoglobin acts as an acid and decomposes the bicarbonate. But this reaction would be comparatively slow if it were not for the enzyme *carbonic anhydrase* which Roughton and his collaborators[137] have found within the erythrocytes. This enzyme accelerates more than a thousand fold the velocity of the reaction: $CO_2 + H_2O \rightleftharpoons H_2CO_3$.

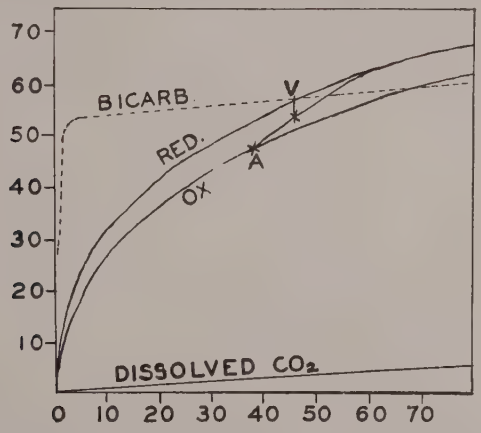


Fig. 251.—Dissociation curves for CO_2 in human blood. Abscissae, CO_2 tension (mm. Hg). Ordinate, CO_2 evolved in vacuo (ml. per 100). *Red.*, completely reduced blood (equilibration against nitrogen and CO_2). *Ox*, oxygenated blood (O_2 tension 100 mm.). *A*, point corresponding to CO_2 and O_2 tensions in arterial, and *V*, in venous blood, in the body. Bicarbonate solution 0.02 molar. (Modified from Peters and Van Slyke.)

The catalytic property is peculiar to the enzyme and is not due to the hemoglobin itself, as was once supposed. The direction of the reaction is determined by the relative masses of the substances participating in it—in this case by the tension of CO_2 in the plasma. As the CO_2 tension is raised, the gas diffuses into the erythrocytes, more H_2CO_3 is formed, and from this bicarbonate ions (HCO_3^-) are split off to combine with alkali made available by a shift of chlorine ions from the plasma into the erythrocytes. As the CO_2 tension is lowered, the reaction proceeds to the left: bicarbonate is decomposed to yield CO_2 and water, and if the CO_2 tension is reduced to zero (as in vacuo) the decomposition is complete and very rapid.

Thus we see why the total amount of CO_2 that can be taken up as bicarbonate varies directly with the tension of CO_2 to which the blood is exposed; it is important to note that most of the CO_2 enters into chemical combination, so that

the acidity of the blood is disturbed as little as possible. But just as increase in the CO_2 tension of the blood helps to turn oxygen out of it and decrease in CO_2 tension assists in reoxygenating it, so increase in the oxygen tension of the blood turns CO_2 out of it and decrease in the oxygen tension makes it capable of carrying more CO_2. This shows again the operation of the general rule that the amount of one respiratory gas carried in chemical combination in the blood varies inversely with the tension of the other gas in the plasma. The rule is illustrated by the curves shown in Fig. 251. Over the range of CO_2 tensions to which blood is ordinarily exposed in the body (40 to 50 mm.) the removal of oxygen from hemoglobin increases by about 5 ml. per 100 the ability of the blood to combine with CO_2 and the addition of oxygen decreases that ability by the same amount. This is a matter of great importance in the transport and elimination of CO_2 because it means that nearly all the CO_2 formed in the tissues

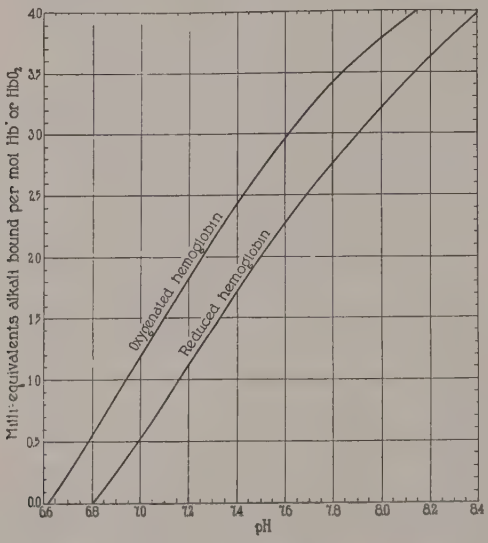


Fig. 252.—Amounts of alkali neutralized by oxygenated and reduced hemoglobin. (From Peters and Van Slyke.)

can be taken up by the blood without any change whatever in the acidity of the blood. Even more important, it means that the oxygenation of hemoglobin in the lungs is largely responsible for the liberation of CO_2 from chemical combination in the blood and its elimination into the alveolar air.

The explanation for this effect of oxygen upon CO_2 combinations is that oxygenation of hemoglobin makes the latter more acid, probably because it increases the dissociation of H-ions from one particular (oxylabile) group of the hemoglobin molecule. Hemoglobin is a protein and, like all proteins, is able to act either as an acid or as a base, depending upon the acidity of the medium; at its isoelectric point it combines with neither acid nor base. The isoelectric point of reduced hemoglobin is at pH 6.8, that of oxyhemoglobin at about pH 6.65. The blood is nearly always more alkaline, the normal pH of the blood cells being 7.25. On the alkaline side of their isoelectric points proteins behave

like acids and can combine with base; the more alkaline the medium, the more base they can bind. This can be measured by determining by titration the amount of base with which the protein can combine, and the results of such determinations with reduced and oxygenated hemoglobin are shown in Fig. 252. As the pH increases (decreased acidity) both oxygenated and reduced hemoglobin combine with more base, as would be expected, but the important point is that oxyhemoglobin always has a greater base-binding capacity than reduced hemoglobin at the same pH. At pH 7.25, which is that of the normal erythrocyte, oxyhemoglobin combines with approximately 2 equivalents of base for each molecule of oxygen taken up. When oxygen is withdrawn, the acidity of the hemoglobin molecule decreases; reduced hemoglobin can combine only with 1.3 equivalents of alkali for each molecule of oxygen given off. This is the main reason why at a given pH reduced hemoglobin can combine with more CO_2 than can oxyhemoglobin. In the lungs the oxygenation of hemoglobin increases its acidity and alkali is withdrawn from combination with bicarbonate to recombine with the hemoglobin itself. Thus for every molecule of oxygen that is given up to the tissues 0.7 molecule of CO_2 can be carried without any change in the pH of the blood. And for every molecule of oxygen taken up by hemoglobin in the lungs 0.7 molecule of CO_2 is liberated from combination with bicarbonate.

At a respiratory quotient $\left(\frac{CO_2 \text{ formed}}{O_2 \text{ consumed}}\right)$ of 0.7 the entire amount of CO_2 produced by the tissues can be taken up and eliminated from the lungs by means of the readjustments produced in the hemoglobin molecule by the removal of oxygen in the tissues and reoxygenation in the lungs. This is a low respiratory quotient: 0.8 is the usual normal one, and quotients of 1.0 are found normally. Consequently there will usually be an excess of CO_2, ranging from 0.1 to 0.3 molecule for each molecule of oxygen consumed, which must be transported and eliminated. The excess can be carried as bicarbonate only if more alkali is withdrawn from hemoglobin or from the plasma proteins. This actually occurs, and the venous blood is more acid than arterial because of it. When exercise is so severe that lactic acid enters the tissue fluid and blood in significant concentration, the respiratory quotient may temporarily rise as high as 2.0. Under such circumstances the excess CO_2 (as well as the lactic acid) is partly neutralized by additional base withdrawn from hemoglobin (which is thereby made to yield more of its oxygen than otherwise), and the venous blood now becomes definitely more acid; at rest the pH of venous blood is 0.03 less than arterial blood, but after violent exercise the difference may be 0.4 or more.

The direct combination of CO_2 with hemoglobin as carbamate is also a reversible reaction: $RNH_2 + CO_2 \rightleftharpoons RNCOOH$. The nature of this reaction is such that its direction is entirely determined by the oxygenation or reduction of the hemoglobin molecule and not by changes in CO_2 tension, which, over the range found in the body, have only a negligible effect upon the amount of CO_2 so combined. When hemoglobin loses oxygen and becomes a weaker acid, its NH_2 groups can bind more CO_2; conversely when reduced hemoglobin takes up oxygen and becomes a stronger acid, its NH_2 groups have less ability to bind CO_2. This carbamate or carbamino-bound CO_2 must not be confused with bicarbonate-bound CO_2 even though most of the alkali for the latter comes from hemoglobin. No enzyme is concerned in the carbamate reaction, but it is intrinsically a very rapid one (Roughton).

The transport of CO_2 may be summarized as follows: Arterial blood (CO_2 tension 40 mm.) is exposed in the tissue capillaries to a higher CO_2 tension and the gas diffuses rapidly into the plasma; it probably does so as dissolved CO_2, not as carbonic acid or bicarbonate which can diffuse through membranes only if a corresponding number of cations diffuse in the reverse direction; there are not enough free cations in the blood or tissues to allow this to occur rapidly and if the CO_2 produced by the tissues were in the form of carbonate or bicarbonate before it entered the blood the transport of CO_2 from the tissues would probably be far too slow for the welfare of the organism (Roughton). As a result of the diffusion the CO_2 tension of the plasma immediately rises and CO_2 diffuses into the erythrocytes. There the reaction, $CO_2 + H_2O \rightleftharpoons H_2CO_3$, catalyzed by carbonic anhydrase, at once proceeds to the right, more bicarbonate ions are formed and they diffuse out into the plasma; in exchange chlorine ions diffuse from the plasma into the erythrocyte and base is thus made available to balance the bicarbonate ions in the plasma. Simultaneously oxygen is liberated from hemoglobin, mainly (80 to 90 per cent) because the oxygen tension of the tissues is lower (40 mm.) than that of the arterial blood (90 mm.), partly (10 to 20 per cent) because the increase in CO_2 tension of the blood makes it more acid and so decreases the ability of hemoglobin to hold oxygen. Reduced hemoglobin is a weaker acid than oxyhemoglobin, to the extent that 0.7 molecule of base is released for each molecule of oxygen that is given up; this base takes up chlorine which diffuses in from the plasma, and base is thus made available in the plasma to combine with the newly formed bicarbonate. The prompt formation of bicarbonate from CO_2 reduces the CO_2 tension and permits more CO_2 to diffuse into the erythrocyte where it is transformed almost instantaneously into H_2CO_3 and thence to bicarbonate. At the same time the amount of CO_2 that can be held in carbamino combination is increased when oxygen leaves hemoglobin. All these reactions reach an equilibrium at the CO_2 tension existing in venous blood (46 mm. at rest, 60 mm. or more during exercise); they are all rapid enough to be practically completed during the one second or so which the blood spends in the tissue capillaries. The blood has taken up about 4 ml. of CO_2 per 100 if the subject is at rest, 10 to 15 ml. per 100 if he is exercising. The acidity of the blood has increased by about pH 0.03 at rest, pH 0.1 or more during exercise.

When the venous blood reaches the lungs, all these processes are reversed. The CO_2 tension of the blood (46 mm.) is higher than that of the alveolar air (40 mm.) and CO_2 immediately diffuses out of the plasma into the alveoli. This starts the reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3$ in motion toward the left within the erythrocytes (carbonic anhydrase) because the reaction had come to an equilibrium at a CO_2 tension of 46 mm.; CO_2 is liberated from the bicarbonate within the erythrocytes and the gas promptly diffuses out into the plasma and thence across the alveolar membranes. Simultaneously oxygen has diffused into the plasma (oxygen tension 40 mm.) from the alveoli (oxygen tension 100 mm.) and thence into the erythrocyte; hemoglobin takes up oxygen and becomes a stronger acid. For each molecule of oxygen taken up 0.7 molecule of base is reappropriated by the hemoglobin molecule. A corresponding number of chlorine ions diffuse out into the plasma. This enables an equal number of bicarbonate ions to diffuse into the erythrocyte where they are instantly broken up (carbonic anhydrase) to yield more CO_2 which promptly diffuses out again. The carbamino-bound CO_2 is diminished because the NH_2 group to which it is attached

has a less firm hold upon it when oxygen is taken up by the hemoglobin molecule. The end result is that the blood loses its extra burden of CO_2 (4 ml. per 100 at rest, 15 ml. or more per 100 during exercise) and emerges from the lungs as arterial blood, with a CO_2 tension of 40 mm. at rest (slightly higher during exercise).

A diagrammatic presentation of the factors concerned in the removal of CO_2 from the blood in the lungs is given in Fig. 253. According to Roughton, the total amount of CO_2 given up by the blood in the lungs (i.e., 4 ml. per 100 ml. of blood, or 200 ml. per minute in a subject at rest with an oxygen consumption of 250 ml. per minute and a respiratory quotient of 0.8) is derived as follows:

About 10 per cent from CO_2 physically dissolved in the plasma.
About 20 per cent from carbamino-bound CO_2.

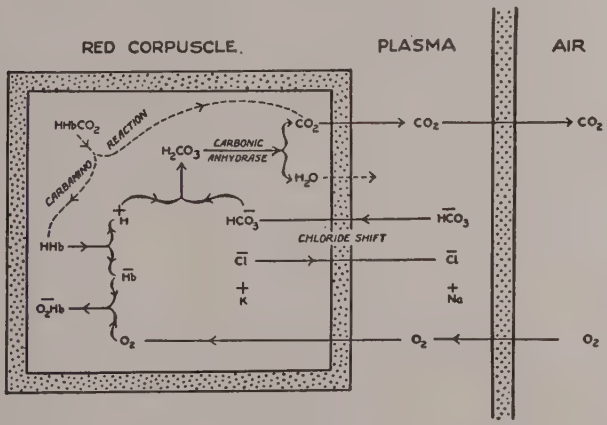


Fig. 253.—Schematic summary of the main processes concerned in the expulsion of CO_2 from blood in the lungs. *HHb*, reduced hemoglobin; *O_2Hb*, oxyhemoglobin. (From Roughton: Physiol. Rev. **15**: 241, 1935.)

About 70 per cent from bicarbonate, all of it yielded because of the action of carbonic anhydrase within the erythrocytes. Roughton calculates that about one-third of the bicarbonate is carried within the erythrocytes, two-thirds in the plasma. He believes that access of the bicarbonate ions of the plasma to the enzyme depends upon an exchange of an equal number of chlorine ions between erythrocyte and plasma; the rate at which this 70 per cent of the total CO_2 is taken up in the tissues or eliminated in the lungs would therefore depend on the rate of this shift of chlorine ions. These deductions have been recently confirmed by Stadie and O'Brien.[153]

THE REGULATION OF THE REACTION OF THE BLOOD

This subject is so closely related to the transport of CO_2 that it can properly be considered now. Many of the factors concerned in it have been mentioned in other parts of this book, but it is well to correlate them at this point.

The fundamental facts are these: In order that the cells of the body may function normally, they must be surrounded by a liquid environment (tissue

fluid and lymph) with a reaction slightly on the alkaline side of neutrality. This reaction is maintained constant in spite of wide fluctuations in the amounts of acid and alkali taken into the body with the food and in the amounts of acid produced by the metabolic processes of the body. The factors responsible for this constancy fall into two main groups: (1) *physicochemical,* and (2) *physiological.* The various factors of the two groups cooperate in such ways that a change in one physico-chemical factor is compensated ("buffered") by other factors of the same group, and if this proves insufficient physiological factors are brought into activity to restore the reaction of the blood to normal.

The range of the reaction of the blood serum compatible with life in man appears to be about from pH 7.0 to pH 7.8, but these are the extreme limits encountered in very abnormal conditions. In normal persons the range is much narrower; i.e., the acidity of the serum varies only between pH 7.4 and pH 7.6; under ordinary circumstances the serum remains at about pH 7.4, and if alkalosis is produced (as by overventilation) symptoms of that disturbance (tetany) appear when or before pH 7.6 is attained.

The Physicochemical Factors.—When a weak acid such as carbonic or phosphoric or a protein exists in solution together with its alkali salts the mixture has the property of taking up H^+ or OH^- ions, i.e., of preventing changes in the pH of the solution, when acid or alkali is added. These are *buffers.* The buffers of importance in the body are dissolved CO_2 and bicarbonate $\left(\frac{CO_2}{BHCO_3}\right)$,* diacid and dibasic phosphate $\left(\frac{BH_2PO_4}{B_2HPO_4}\right)$, and proteins and alkali proteinate, hemoglobin being by far the most important of the protein buffers $\left(\frac{HHb}{BHb}\right)$. All of the powers of the body to neutralize acid reside in these buffers; the salts of strong acids (chlorides, sulfates, etc.) are not available for the purpose because such acids have too strong an affinity for the combined base to part with it under any conditions compatible with life, and free alkali cannot exist in the body. Since all the buffer groups are necessarily mixtures of acid and base it is proper to use the term acid-base balance of the blood as a synonym for the physicochemical defense against changes in its normal reaction. Of the factors concerned in the acid-base balance the $\frac{CO_2}{BHCO_3}$ equilibrium is by far the most important, both quantitatively (it can neutralize more than 60 per cent of any acid other than carbonic, though it cannot of itself neutralize CO_2) and qualitatively (because the acid is volatile and its elimination from the body is adjusted through the respiratory center according to the tension of CO_2 in the blood). Consequently the amount of bicarbonate in the blood gives a trustworthy picture of the amount of alkali available to neutralize acid, i.e., the alkali reserve. It can be determined simply and accurately by equilibrating the blood against alveolar air (CO_2 tension = 40 mm.) and determining the amount of CO_2 contained in the blood by means of the Van Slyke apparatus.

*The situation with regard to CO_2 is peculiar. CO_2 is not an acid in itself since no hydrogen ions can arise from it. Yet it is now known that true carbonic acid (H_2CO_3) represents only about 1/1000 of the total free CO_2 of a solution of the gas in water or blood. It is also known that H_2CO_3 is a powerful acid (about as strong as acetic) whereas CO_2 is not acid at all. Formerly all of the dissolved CO_2 was thought to be as H_2CO_3, and this was supposed to be only about 1/1000 as strong as true carbonic acid is now known to be. No misunderstanding need arise if we let the symbol CO_2 represent total free CO_2, of which only about 1/1000 is in the form of H_2CO_3; from this small proportion come the hydrogen ions responsible for the acidity and buffer properties of the mixture.

If a nonvolatile acid appears in the blood, it immediately reacts with bicarbonate as follows: $HCl + NaHCO_3 = NaCl + H_2CO_3$. An increase in the amount of carbonic acid starts the reaction $CO_2 + H_2O \rightleftharpoons H_2CO_3$ in motion to the left and the excess becomes CO_2; the sodium salt is neutral. The CO_2 is promptly excreted by the lungs. Other acids are eliminated by the urine, and this process takes more time. At the normal plasma pH of 7.40 the proportions of $\frac{CO_2}{BHCO_3} = \frac{1}{20}$. The introduction of a fixed acid reduces the amount of $BHCO_3$ and this would make the blood more acid, but as soon as this happens the CO_2 tension increases and breathing is stimulated. CO_2 is thus removed until the ratio $\frac{CO_2}{BHCO_3}$ again becomes $\frac{1}{20}$; although the actual amounts of $BHCO_3$ may now be considerably less than before, as long as the ratio remains unchanged the pH is unaltered. Chlorine ions diffuse into the erythrocytes whenever the number of other anions in the plasma increases, and this makes base available in the plasma for combination with the newly introduced acid. Hemoglobin yields more of its oxygen at a given oxygen tension if the acidity of the plasma is increased, and this releases more alkali from combination with hemoglobin. The phosphate buffers and the plasma proteins can yield only negligible amounts of alkali for combination with a foreign acid.

Ordinarily fixed acids do not appear in the blood in significant amounts; it is only during violent exercise (lactic acid), severe diabetes (β-oxybutyric and acetoacetic acid), starvation (the same acids as in diabetes), or severe anoxemia (lactic acid) that fixed acids appear in sufficient quantity to deplete the alkali reserve by combining with the base of bicarbonate to form salts that are excreted in the urine. Under normal conditions CO_2 is the only acid with which the blood has to deal in appreciable quantities, and always there is more of this than of any other acid. The reactions concerned in dealing with CO_2 formed in the tissues are as follows:

1. Combination with NH_2^- groups of hemoglobin.
2. Combination with base derived from the reduction of oxyhemoglobin.
3. Combination with base made available by a shift of chlorine ions from plasma into erythrocytes.
4. Combination with base derived from the phosphate buffers:

$$H_2CO_3 + Na_2HPO_4 \rightleftharpoons NaHCO_3 + NaH_2PO_4.$$

Actually phosphates are present in the blood in such minute amounts that they cannot have more than a negligible buffer action. In the urine they are concentrated and are much more important.

5. Combination with blood proteins other than hemoglobin:

H_2CO_3 + NaProteinate $\rightleftharpoons$ $NaHCO_3$ + H-Proteinate. This also is negligible.

According to Peters and Van Slyke (page 894) the alkali available for the neutralization of acids other than carbonic is distributed among the buffer groups of the blood as follows:

	MILLIEQUIVALENTS PER LITER
Bicarbonate alkali	18
Hemoglobin alkali	8
Other buffer alkali	2
Total	28

The serum proteins can yield about 1.7 milliequivalents of alkali per liter when the pH is reduced from 7.4 to 7.0, so that most of the "other buffer alkali" is furnished by them. Counting the circulating blood volume as a little more than 5 liters, the physiologically available alkali of the blood should be able to neutralize about 150 ml. of acid of 1N strength.

The great importance of bicarbonate as a defense against acid depends upon the fact that when another acid is introduced and bicarbonate is decomposed, its acid radical can be eliminated promptly by the lungs. For this reason as much as 80 per cent of the bicarbonate of the blood can be decomposed before severe acid poisoning results. But when the acid is carbonic—as it normally is—hemoglobin is the buffer of paramount importance.

The Physiological Factors.—The important agencies in this connection are the pulmonary ventilation and the renal output of acid and base.

The *pulmonary ventilation* is closely adjusted according to changes in CO_2 tension of the arterial blood. When there is a reduction in the denominator of the fraction $\frac{CO_2}{NaHCO_3}$ because of introduction of an acid other than carbonic, the hydrion concentration of the blood increases and the CO_2 tension rises. Breathing is at once stimulated and remains so until the numerator (CO_2) is reduced to correspond with the reduction in the denominator ($NaHCO_3$); when the ratio is again 1:20 (it may now be 0.5:10 or even 0.25:5) the CO_2 tension is restored and breathing quiets down again. If the acid responsible for the change is CO_2, the numerator of the fraction increases first, but the denominator is also increased by alkali made available by the passage of chlorine into the erythrocytes; breathing is again stimulated, but it returns to normal when the ratio of carbonic acid to bicarbonate is again 1:20, though this may now mean a ratio of 1.5:30 or 2:40. Conversely, when alkali is introduced into the blood, breathing is depressed until enough CO_2 is retained to restore the ratio to the normal 1:20; if CO_2 is lost (as at high altitudes or in any hyperpnea due to something other than increased CO_2 tension in the blood) there is a relative excess of $NaHCO_3$, and this is taken care of at least in part by excretion of an alkaline urine.

The *kidney* compensates mainly by altering the balance between the acid (NaH_2PO_4) and basic (Na_2HPO_4) phosphates excreted in the urine. On an ordinary mixed (meat-containing) diet the urine is acid, i.e., there is a relative excess of NaH_2PO_4. On a vegetable diet the urine is alkaline, Na_2HPO_4 being in excess. Whenever there is an excess of acid in the body the NaH_2PO_4 is excreted in larger proportion and when there is an excess of alkali the Na_2HPO_4 predominates; as we have just seen, this takes place at high altitudes and under any other condition in which overventilation occurs.

The ammonia mechanism makes NH_3 available for combination with abnormal acid, as in the acidosis of diabetes, instead of excreting the nitrogen as neutral urea. The ammonia neutralizes acid that would otherwise demand alkali of the blood and the latter is thus spared to some extent. When there is a relative excess of alkali in the blood, ammonia excretion diminishes or ceases and other alkali is excreted instead. This mechanism comes into play very slowly, i.e., after several days of acidosis or alkalosis.

Acidosis and Alkalosis.—The mechanisms which we have just considered are so effective that ordinarily the hydrion concentration and bicarbonate content of the blood remain remarkably constant, the former at about pH 7.4, the

latter at a plasma CO_2 combining capacity of about 60 ml. per 100. There may be temporary changes associated with muscular activity, ingestion of acid or alkali, or voluntary interferences with normal breathing, but these are fully and promptly recovered from by normal persons. In a number of diseases, however, the body defenses against poisoning by acid or alkali are strained more or less severely and if they break down *acidosis* or *alkalosis* results. Both are abnormal and both (unless produced intentionally for experimental purposes) are serious. *Acidosis* means excess acid in the body, *alkalosis* signifies excess alkali. Strictly speaking, acidosis is present only when the blood is less alkaline than normal (pH below 7.4) and alkalosis when the blood is more alkaline than normal (pH above 7.4). Actually, however, there may be sufficient poisoning by acid or alkali excess to produce definite symptoms before the reaction of the blood has changed. As long as the hydrion concentration of the blood remains within normal limits, the acidosis or alkalosis is *compensated*. When the poisoning becomes too severe for the defense mechanisms to compensate and the hydrion concentration changes, the acidosis or alkalosis is *uncompensated* and the condition is usually a very serious one.

We have seen that the maintenance of the hydrion concentration of the blood depends upon a balance between weak acids and their alkali salts (CO_2-bicarbonate, hemoglobin-hemoglobinate, diacid-dibasic phosphates, protein-proteinate), for it is only such mixtures that can act as buffers. As already pointed out, to speak of the *acid-base balance of the blood* is the equivalent of listing the physicochemical reactions concerned in the regulation of the reaction of the blood. Acidosis then becomes a disturbance of the acid-base balance toward the acid side, alkalosis a disturbance toward the alkaline. But a disturbance toward the acid side may be due either to a primary excess of acid or to a primary deficiency of alkali; as the condition occurs clinically both factors usually are involved simultaneously. Similarly a disturbance toward the alkaline side may result from a primary excess of alkali or from a primary deficiency of acid; clinically the latter is the more frequent cause. We have seen that the $\frac{CO_2}{NaHCO_3}$ buffer system is the first and most important defense of the body against poisoning by acid (other than carbonic) or alkali because changes in bicarbonate lead to compensatory changes in the elimination of CO_2 by the lungs and the ratio of acid to base is thus readily restored. Consequently the amount of bicarbonate in the blood gives a direct and accurate picture of the status of the acid-base balance in general and the amount of bicarbonate (measured by the capacity of the blood to combine with CO_2) decreases in acidosis and increases in alkalosis, provided that the acidosis or alkalosis is due to changes in acid or alkali other than CO_2 itself. If an acidosis is due primarily to retention of CO_2 the blood bicarbonate increases, and if an alkalosis is due primarily to excessive loss of CO_2 the bicarbonate decreases.

A definite change in the bicarbonate content of the blood usually occurs long before the hydrion concentration has become abnormal. Because this change occurs early and is easily detected in changes in the CO_2 combining power of the blood plasma, most clinical states of disturbance in the acid-base balance of the blood can properly be classified as conditions of *alkali deficit* or *alkali excess*. The corresponding disturbances due primarily to retention or loss of CO_2 must be kept distinct, however, and classified as states of CO_2 excess or CO_2

deficit. A *compensated alkali deficit* is one in which the loss of bicarbonate is balanced by increased elimination of CO_2 and the hydrion concentration of the blood is unchanged; a *compensated alkali excess* represents a corresponding retention of enough CO_2 to keep the blood reaction from becoming abnormally alkaline. An *uncompensated alkali deficit* is present when the reduction in bicarbonate is too great to be counteracted by increased elimination of CO_2 and the blood becomes more acid; an *uncompensated alkali excess* is produced by absorption of too much alkali, or loss of too much acid, to be counteracted by retention of CO_2, and the blood is abnormally alkaline.

Primary alkali deficit is the commonest type of abnormality of the acid-base balance. It is seen in characteristic form in the acidosis of diabetes mellitus or advanced nephritis. In diabetes the primary factor is excess of abnormal fixed acids (β-oxybutyric, acetoacetic) resulting from incomplete oxidation of fats; these combine with the alkali of the blood and the combinations are excreted in the urine. The bicarbonate of the blood is thus reduced. At the same time the output of urine is increased because of the increased amount of material to be eliminated, and ammonia excretion is also greatly increased; the body loses salts and water and becomes dehydrated. Thus in this condition there is both acid excess and alkali deficit, but the former is the primary factor. In nephritis the kidney is unable to excrete the fixed acids normally formed in metabolism and their retention leads to reduction in the bicarbonate of the blood. Experimentally a condition corresponding to primary alkali deficit can be produced by ingestion of large amounts of acid-forming salts such as ammonium chloride (15 to 20 grams) or calcium chloride (25 to 30 grams) (the ammonia becomes urea in the body and an excess of Cl is thus created; Ca is excreted by the intestines leaving the Cl behind in the blood). In all such cases, clinical and experimental, the outstanding symptom is dyspnea; there is also polyuria and the ammonia excretion in the urine increases. In terminal diabetic acidosis respiration becomes more and more dyspneic and finally takes on the agonal character known as "air hunger." In starvation there is an acidosis similar to that of diabetes and due to the same cause, i.e., incomplete combustion of fats. Acidosis also occurs in poisoning by methyl alcohol (CH_3OH), which is oxidized to formic acid (HCOOH) in the body and the latter is excreted in the urine in combination with alkali (HCOONa). An acidosis similar to that of diabetes (ketosis) is sometimes produced intentionally by a special ketogenic diet in the treatment of epilepsy, the seizures of which have been found to be reduced in some subjects by this procedure.

Primary alkali excess is encountered clinically only as the result of loss of acid from the body, as in the vomiting of pyloric or intestinal obstruction (HCl is lost in the vomited gastric contents); in some cases of infantile diarrhea there may be a relatively greater loss of acid than of alkali, while in others the reverse may be true; i.e., either alkali excess or alkali deficiency may result, the urine being alkaline in the first case, acid in the second. Alkali excess can of course be produced by ingestion of alkali. The result of primary alkali excess is the same no matter how it is produced: there is an increase in the bicarbonate of the blood, breathing is apt to be depressed, or at least the breath can be held for an unusually long time, alveolar CO_2 tension tends to rise, the urine becomes alkaline and its ammonia content decreases; if the blood becomes definitely alkaline (pH 7.6) tetany is likely to occur.

Primary CO_2 excess is unimportant practically. It can occur in disease only when the gas exchange is markedly interfered with, and then the anoxia which occurs simultaneously is much the more serious condition. It may of course be produced intentionally by inhalation of CO_2 either for experimental purposes or to combat respiratory depression. It occurs when the respiratory center is depressed by narcotics (morphine, ether, alcohol, barbiturates, etc.) but breathing continues only because the CO_2 tension of the blood rises and the O_2 tension falls; the anoxia is the dangerous feature, not the CO_2 excess (see Chap. XLIV). Peters and Van Slyke state that "It is doubtful that (medical and lay literature) contains any case of death due primarily to impaired respiratory ability to excrete carbonic acid."*

Primary CO_2 deficit occurs whenever respiration is driven by some agent other than the normal chemical stimulus (carbon dioxide tension in the center). Thus it results from the hyperpnea of anoxemia (as at high altitudes), of fever, or of high temperature produced by external heat; it is occasionally seen in encephalitis when respiration is increased for long periods of time presumably because the disease involves excitation of the cells of the center. In all such cases the CO_2 tension of the blood is reduced and the blood tends to become more alkaline; if the latter change proceeds far enough (to pH 7.6) tetany may occur. The urine becomes more alkaline due to increased excretion of base, and the blood bicarbonate falls; this is the main compensatory factor, and it usually succeeds in restoring the pH of the blood nearly if not quite to normal.

*The rapidly increasing use of solidified CO_2 ("dry ice") carries with it hazards which have long been recognized by miners and well-diggers but of which the general public is still unaware. The United Press on November 25, 1936, distributed an account (see the Philadelphia Inquirer of that date) of the death in New York of 5 men who were overcome by "dry ice" fumes while unloading frozen cherries from the hold of a ship; two others recovered. Accidents of this nature have often happened in mines and in wells and it has long been known that CO_2 accumulates in low, poorly ventilated places because it is heavier than air. When there is a high proportion of CO_2 in the inspired air, the individual exposed to it is in danger both from the narcotic effects of CO_2 (see page 563) and from the anoxemia resulting from reduction in the proportion of oxygen in the air. Volatilization of solidified CO_2 in a poorly ventilated space will lead to a marked rise in the CO_2 content of the air, particularly near the bottom of the space, thus reproducing the conditions which are found in mines as a result of the oxidation of coal or other organic material, in wells as a consequence of fermentations and oxidations carried out by plants, molds, and bacteria.

CHAPTER XLIV

ABNORMAL TYPES OF RESPIRATION

Our considerations of the control of respiration, hitherto confined to the normal state, have now proceeded far enough to warrant an attempt to apply them to the various conditions in which an abnormality of breathing is a matter of concern either to the afflicted person or to those attending him. Obviously it is under the latter circumstances that the practical importance of these considerations is greatest, and as far as the practicing physician is concerned the ensuing section is the climax of respiratory physiology. I believe that our understanding of the factors that may contribute to respiratory control has advanced sufficiently to permit us now to approach this subject by deriving first from theoretical grounds the abnormalities that might be expected and then to cite actual examples of these as they occur in the course of disease; this is the viewpoint from which the following section has been compiled.

DYSPNEA

According to Meakins, "Dyspnea is the consciousness of the necessity for increased respiratory effort." The outstanding feature is therefore an element of discomfort, usually a sensation of breathlessness, on the part of the subject. In terms of our present understanding of the interplay of factors operating in the respiratory center (page 601), this means that the discharge of impulses by the inspiratory neurons does not diminish or disappear as it should at the end of inspiration but persists throughout the respiratory cycle and the desire to breathe therefore is not satisfied even by abnormally powerful respiratory efforts. As far as objectively demonstrable characteristics are concerned, *dyspnea* (labored breathing) differs from *eupnea* (quiet breathing) in that the accessory inspiratory and the expiratory muscles participate actively in the respiratory act during dyspneic breathing (page 556). *Hyperpnea* (hyperventilation) is a related term denoting simply an increase in pulmonary ventilation without commitment as to subjective sensations or character of breathing.*

Theoretically dyspnea might be due to any one or more of the following factors: (1) increase in the chemical stimulus acting on the center; (2) in-

*It may be well to direct the reader's attention to some of the difficulties involved in the literal acceptance of these definitions, for the vexatious problem of terminology in physiology is well illustrated here. According to Meakins' definition, as Christie[35] points out, dyspnea could not occur in comatose or anesthetized subjects, and even greater absurdities may result unless the definition is accorded reasonable flexibility (see Christie[35]). The distinction between dyspnea and hyperpnea can be based only upon subjective factors; since the accessory inspiratory and expiratory muscles are active in both conditions the difference between hyperpnea and dyspnea must either be made on an arbitrary basis of degree of increase in respiratory activity or in terms of the subject's sensations. Dyspnea can occur without increased pulmonary ventilation; reduction of the latter is in fact a common cause of dyspnea (see below). On the other hand, increased ventilation can be produced by artificial means without discomfort, as by artificial respiration or intratracheal insufflation; subjects who have been in the Drinker respirator (page 706) describe the sensations as being entirely pleasant when pulmonary ventilation is thus artificially carried out even though the ventilation is so excessive that the respiratory neurons are inactive and there is no desire to breathe. Thus dyspnea and hyperpnea are not synonyms. The value of the term "dyspnea" lies, as Christie points out, in its clinical implications, and no confusion need arise if this term is always used to imply a situation in which some abnormality of the respiratory system (in the broad sense—page 534) has become severe enough to arouse concern on the part either of the subject or of the observer. Hyperpnea should be restricted to voluntarily or artificially induced respiratory reactions.

crease in the excitatory nerve influences to the center; (3) increased excitability of the center; (4) decrease in the mechanical efficiency of the respiratory act; (5) adverse changes in the circulation, either in the lungs or in the center. As will be seen, examples of each of these may be encountered clinically; the reader will find the ensuing section easier to understand in terms of the general schemes of the entire respiratory process (page 535) and of the interaction of central and reflex factors in the control of breathing (page 601).

1. **Dyspnea Due to Increase in the Chemical Stimulus Acting on the Respiratory Center.**—In this category we find any dyspnea resulting from an increase in the carbon dioxide tension in the arterial blood. This can occur from retention of the carbon dioxide produced in the body whenever the pulmonary gas exchange is interfered with (i.e., in *asphyxia*), but in such cases anoxemia will also be present and will contribute (through chemoreceptor reflexes) to the respiratory response. Dyspnea due entirely to increased CO_2 tension can of course be produced by inhalation of air or oxygen enriched with CO_2 (Fig. 214, page 541), but even here chemoreceptor reflexes would play a part in any except mild effects.

In the dyspnea of acidosis increased carbon dioxide tension probably accounts for much or all of the effect in the early stages (i.e., in *compensated* acidosis; see page 645); when the condition is more severe and the hydrion concentration of the blood increases (*uncompensated* acidosis) chemoreceptor reflexes probably come into play, and these may be entirely responsible for the agonal, "air-hunger" type of dyspnea seen in extreme acidosis. In most cases of dyspnea occurring in the course of disease in man (excepting terminal states when breathing is failing) the carbon dioxide tension of arterial blood is below the normal level.

2. **Dyspnea Due to Increase in the Excitatory Nerve Influences to the Respiratory Center.**—Even now we can place under this category a larger proportion of clinical cases of dyspnea than under any other, and future developments are likely to add to these at the expense of the others until eventually perhaps all forms of dyspnea in disease will be explained on this basis. Here we must include:

a. *Reflexes From the Carotid and Aortic Chemoreceptors.*—Since these account for some of the dyspnea produced by rising CO_2 tension in the blood, and probably for all of that elicited by arterial anoxemia (page 586), it is clear that this is a major factor in the dyspnea of asphyxia however elicited. Asphyxia may be produced by inhalation of air that is abnormally rich in CO_2 or abnormally poor in oxygen (as in wells or mines, or during anesthesia by nitrous oxide or ethylene, or at high altitudes, CO_2 being of course not abnormally high in the latter cases). It may result from obstruction to the free movement of air in and out of the lungs because of inflammatory or neoplastic processes, exudates or secretions, foreign bodies, occlusion of the glottis for any cause, abnormal contraction of the bronchial muscles (asthma), encroachment on the lumen of the finer air passages by engorged blood vessels, or partial or complete paralysis of the respiratory muscles. It may also result from interference with the free diffusion of gases between the air and the blood in the lungs, either because of reduction in the available surface (by rupture, collapse, adhesion, or consolidation of alveoli, or occlusion of pulmonary blood vessels), or because of decreased permeability of the membrane by reason of actual thickening or the introduction of an abnormal layer of fluid

(as in certain forms of pneumonia and in congestive heart failure). Apart from asphyxia, the dyspnea of acidosis may also be due partly (or even entirely) to chemoreceptor reflexes. Perhaps this is also true of the dyspnea associated with fever, but the experimental evidence in support of this is at present quite scanty (page 591), and the idea must be viewed as highly speculative. Finally, the dyspnea encountered in poisoning by cyanides, sulfides, nicotine, lobeline, coniine, etc., is referable entirely to chemoreceptor reflexes.

b. *Reflexes From the Lungs.*—Whenever the alveoli are no longer normally distended the excito-inspiratory Hering-Breuer reflex is brought into action in the undistended parts, and since the receptors are of the slowly adapting type the excitatory influence thus aroused will continue as long as the subnormal inflation persists. Thus the dyspnea of pneumothorax, and the wholly analogous effect of atelectasis produced by obstruction of a bronchus, can be accounted for. Interference with the circulation in the blood vessels in the alveolar walls (as by embolization of the pulmonary arterial branches or thrombosis on the pulmonary venous side) is followed by partial collapse of some of the alveoli, and this probably explains the marked acceleration of breathing observed by Binger, Brow and Branch[24] when they injected starch particles intravenously in dogs—an effect that they found to be abolished by blocking the vagi and to be related to decrease in the size of the alveoli amounting in some places to actual collapse. In any case, failure of the lungs (or of any considerable part of them) to expand properly with inspiration will diminish the strength of the inhibito-inspiratory influence set up by inflation of the lungs and this may account for lack of satisfaction of the urge to breathe even by the maximum inspiratory effort.

According to Christie,[35] and Harrison,[70] the dyspnea of heart disease in man is probably due to increased rigidity of the lung consequent upon pulmonary congestion. This rigidity presumably leads to continuous stimulation of the excito-inspiratory Hering-Breuer reflex and thus to the sensation of breathlessness. Most patients with congestive failure of the heart are least uncomfortable in the sitting position *(orthopnea),* which may be related to the facts that diminution in the vital capacity of the lungs is present in cardiac dyspnea and that the vital capacity is greatest in the sitting position (page 543). These observations probably are to be interpreted as follows: congestion in the pulmonary circuit (resulting from a relative insufficiency of the right ventricle) causes rigidity of the lung, which is manifested in (and can be measured at least approximately by) reduction in the vital capacity, indicating a diminution in the extent to which the pulmonary tissues are expanded at inspiration. This, through continuous stimulation of the excito-inspiratory Hering-Breuer reflex, causes dyspnea; in the upright position the vital capacity is increased and therefore (presumably) the pulmonary congestion is decreased correspondingly; the respiratory distress is diminished because the pulmonary tissues are now expanding better with inspiration, and the urge to breathe, which previously did not cease even at the height of inspiration (presumably because the alveolar ducts did not enlarge sufficiently to abolish the excito-inspiratory discharge from one set of Hering-Breuer receptors and to set up an effective inhibito-inspiratory discharge from the other), now can diminish as it normally does during inspiration, and the sensation of breathlessness (i.e., of being unable to satisfy the urge to breathe even by a maximal inspiratory effort) decreases correspondingly.*

Whether any other reflexes from the lungs or the pulmonary blood vessels play a part in dyspnea remains to be determined. If our conception of the embryological significance

*It is perhaps significant in this connection that morphine, which is notable for its ability to relieve the dyspnea of heart disease, appears also to be notable for its ability to exaggerate inhibitory reflexes to respiration.[74, 139] The action apparently is central and may be due to a primary decrease in the sensitivity of the central neurons to the chemical stimulus, but the end result is to increase the effectiveness of inhibito-inspiratory influences. This may account in part for the diminution in the breathlessness of these patients when given morphine, but the removal of unpleasant sensations for which this drug is justly famous can certainly not be overlooked as an important factor in the relief produced by it in such patients.

of the carotid and aortic chemoreceptors is valid (page 597), then the derivation of the pulmonary artery from the sixth branchial arch arteries and the demonstration by Nonidez[21] that this vessel, in newborn animals, may supply tissue having the morphological characteristics of chemoreceptors, assume deeper significance. A search for chemoreflex mechanisms that would come into play only under abnormal conditions of pressure or flow in the pulmonary circulation might disclose something of this sort as an important factor in cardiac dyspnea. At present there is no information on this subject except that reported by Daly,[45] who found some evidence of a pressoreflex system in the pulmonary artery of the dog; the reflex effects from this system seem altogether too weak to justify the belief that severe dyspnea could ever be produced by it. Reflexes from the muscles or joints of the thoracic wall may also be a factor in dyspnea, but this has not yet been demonstrated to be the case. Yet it is only fair to point out that much remains to be learned about the physiology of cardiac dyspnea and perhaps postural reflexes are more important than they are now thought to be. Wood[170, 171] has found that some of these patients are least dyspneic when lying on one side, some on the other, and some when in the face-down position. Perhaps the congestion in the pulmonary circulation is best relieved by a position that varies from individual to individual, for reasons as yet unknown; or perhaps some other reflex factors (also unknown) are involved.

3. **Dyspnea Referable to Changes in Excitability of the Central Neurons.**—As we have already seen (page 604) this factor now appears to be the dominant one in respiratory control, but it is impossible to draw any hard and fast distinction between it and excitatory reflexes. From the standpoint of the physiology of dyspnea, we may include here:

(a) *Irritative Lesions Impinging Directly Upon the Medullary Reticular Formation, or Located Elsewhere in the Neuraxis and Giving Rise to Impulses Excitatory to the Respiratory Neurons.*—This probably accounts for the hyperpnea sometimes observed in patients with encephalitis or other types of intracranial disease. Between this and the hyperpnea, breathlessness, or respiratory discomfort that may be associated with functional neuroses the only distinction is that the lesions in the latter presumably are purely biochemical or biophysical and leave no demonstrable mark in the neuraxis. The result is the same as though the excitatory impulses which normally arise only when there is need for increased pulmonary ventilation (as in exercise—page 603) were bombarding the respiratory neurons.

(b) *Increased Metabolic Rate in the Respiratory Neurons.*—This is a theoretical possibility the actual importance of which can only be conjectured (see page 568). The respiratory effect would be attributed to an increase in the number of molecules of carbon dioxide within the central neurons because of an increase in the rate at which CO_2 is being produced by them. The hyperpnea associated with increased body temperature might be due to this factor and so might that elicited by drugs and poisons which increase nerve cell activity in general (the so-called analeptics, including strychnine, caffeine, camphor, atropine, picrotoxin, metrazol, coramine, hexeton-drugs which have the common property of producing convulsions when given in sufficiently large amounts and whose actions on respiration, as far as is known, are entirely due to direct effects on the neuraxis, not to reflexes*). These drugs presumably combine with the neuronal protoplasm so as to produce the same sort of increase in excitability that carbon dioxide brings about.

The converse of this relation (depression of breathing attributable to decreased excitability of the center) is encountered in hibernating animals[128] and

*Coramine is a partial exception to this, for the hyperpnea produced by it is said to be partly due to chemoreceptor reflexes, partly to a direct central action.

in human beings in which similar processes are artificially induced by depressant drugs (see page 683) or by reducing the body temperature.[149, 150] It is probable that the fundamental factor in these cases is reduction in the metabolic rate of the cells of the neuraxis; whether the ensuing respiratory depression is due to removal of excitatory impulses previously playing upon the respiratory neurons but arising elsewhere, or to decrease in the oxidative reactions within the respiratory neurons themselves, is entirely conjectural.

4. **Dyspnea Due to Changes in the Mechanical Efficiency of the Respiratory Movements.**—This special section accommodates those dyspneas in which the chest has assumed a position close to that of full inspiration and is capable of further enlargement only by means of strong contraction of the accessory inspiratory muscles. This is the situation in *emphysema.* The breathlessness often encountered in this condition probably means that the Hering-Breuer reflex system is perverted much as it is in cardiac dyspnea, i.e., the excito-inspiratory reflex is continually active because of shortening of a considerable number of the corresponding receptors in some parts of the lungs. This could result from the breaking of alveolar septa at one end, allowing the other to retract and thus to shorten these receptors. At inspiration these parts of the lungs could not stretch enough to terminate this discharge. The inhibito-inspiratory reflex also would not be as effective as it should be both because the receptors that are active are not stretched as much as normally at inspiration (by reason of the relative smallness of the further thoracic enlargement that can be produced in an emphysematous chest), and because a considerable proportion of them would be permanently inactivated by the same alveolar changes that lead to a continuous excito-inspiratory discharge from the other set of receptors. When the movements of the chest are sufficiently interfered with to lead to inadequacy of pulmonary ventilation asphyxia of course ensues and dyspnea is then contributed to by the other factors noted above in connection with asphyxia. It is noteworthy that (according to Nielsen[119]) the cost of pulmonary ventilation in man (i.e., the fraction of the body's total oxygen consumption that is due to the activity of the respiratory muscles) is least during quiet breathing and increases sharply during dyspnea; during quiet breathing the respiratory muscles accounted for about 1.3 per cent of the total oxygen consumption, but during the dyspnea of exercise this proportion rose to 9 per cent of the total. Thus it would seem that the accessory inspiratory and the expiratory muscles are relatively inefficient compared with those of quiet breathing, and any condition in which pulmonary ventilation must be brought about entirely by them necessarily entails an undue amount of exertion.

5. **Dyspnea Due to Changes in the Circulation.**—Here we may consider all of the circulatory abnormalities that can lead to inadequate flow of blood through the lungs or tissues (particularly the respiratory center itself) as well as insufficiencies on the part of the gas-transporting medium itself (hemoglobin).

(a) *Faulty Circulation Through the Lungs.*—This condition may lead to dyspnea when it is either too sluggish or too rapid. As we have already seen, too sluggish circulation leads to engorgement of the pulmonary system, increases the rigidity of the lung, and, by the diminished respiratory excursion thus brought about, apparently gives rise to reflexes excitatory to respiration. Too rapid circulation through the lungs, on the other hand, may shorten the time permitted for the pulmonary gas exchange to the point at which anoxemia

ensues. When we recall that even under normal conditions the blood does not come to equilibrium with the alveolar air with respect to oxygen but reaches the tissues with the hemoglobin only about 95 per cent saturated with oxygen and with the arterial tension of the gas about 10 mm. lower than that in the alveolar air (Chapter XLII), it is evident that a further acceleration of the flow of blood could easily increase this discrepancy. Ordinarily when such acceleration occurs (as during exercise) it is compensated to a considerable extent by increases in the diffusion constant for oxygen (page 620) and in the alveolar oxygen tension (consequent upon deeper breathing—page 618). This is not the case in disease conditions in which, by reason of interference with the circulation through part of the pulmonary system, the intact parts of this system must accommodate a larger proportion of the total cardiac output. Even the highest alveolar oxygen tension attainable in the intact alveoli by increased breathing of ordinary air may then be inadequate. Such a situation can exist in emphysema, atelectasis, lobar pneumonia, or occlusion of the arterial or venous supply of parts of the alveolar system for any cause. The actual dyspnea in such cases would probably be referable to reflexes aroused either in the lungs by the deranged relations of the Hering-Breuer receptors, or in the chemoreceptors by the anoxemia. It is unlikely that increase in the chemical stimulus acting directly on the center would be a factor here because of the greater diffusibility of carbon dioxide than oxygen; there is much less likelihood of the blood failing to unload its CO_2 properly in the lungs than there is of its being inadequately saturated with oxygen under such circumstances, and the CO_2 tension of arterial blood would probably fall in consequence of the increased pulmonary ventilation brought about reflexly.

(b) *Faulty Circulation Through the Tissues as a Whole May Cause Dyspnea Because of the Presence of Acid Products of Incomplete Oxidation.*—Such products on entering the blood in sufficient amounts, would increase the carbon dioxide tension and thus stimulate breathing centrally (perhaps also in the chemoreceptors); if severe enough, chemoreceptor reflexes may be set up by the increased acidity itself, thus intensifying the dyspnea. Perhaps reflexes excitatory to breathing may also arise in tissues suffering from an inadequate flow of blood. The experiments of Alam and Smirk[6] strongly suggest that this can occur, but further investigation is needed before the importance of this factor can be surmised.

(c) *Faulty Circulation Through the Respiratory Center Itself.*—Dyspnea due to this factor is illustrated by the violent respiratory response of a reactive animal to abrupt occlusion of the four main arteries leading to the brain (Fig. 254); such an effect is doubtless due to sudden accumulation in the cells of the center (or in other neurons capable of setting up impulses strongly excitatory to these) of metabolic products the concentration of which becomes stimulant when the circulation suddenly becomes inadequate to carry them away as rapidly as they are formed. The clinical counterpart of this must be very rare, for dyspnea occurs in animals only if an extreme reduction in blood supply takes place suddenly and the central neurons are not greatly depressed (by narcosis, anoxia, etc.) at the time of the reduction; a similar situation would be expected in man only in cases of sudden occlusion or rupture of major arteries in the medulla. Conditions in which respiration is strongly influenced by changes in the cerebral circulation may, however, be much commoner than this. For one thing, it is not unlikely that, by interference with the venous

return from the brain, sufficient accumulation of carbon dioxide can be brought about to lead to dyspnea; this has been suggested in the past as a possible cause of cardiac dyspnea, but the burden of evidence has been against it, largely because no conclusive experimental evidence was ever presented that such a relation actually could exist. The negative outcome of experiments intended to test this probably is due to the fact that the cerebral venous system communicates freely not only with the channels leading directly from the head to the superior cava, but also with the spinal venous sinuses; since the latter are drained by numerous veins throughout the length of the vertebral canal,

Fig. 254.—Effect of acute cerebral anemia on respiration. Cat: barbital narcosis. Respiration recorded by plethysmograph, blood pressure by mercury manometer. Tracing just below blood pressure shows pressure in circle of Willis, recorded from cephalic ends of vertebral arteries, which are ligated at their cardiac ends. *A*, occlusion of carotid arteries until respiration failed. *B*, briefer occlusion. Note marked stimulation of breathing in both cases. Blood pressure usually rises more than in this animal, in which pulse slowed markedly as a result of the anemia.

occlusion of the jugular and vertebral veins, even complete ligation of the superior cava close to the heart, produces only a relatively slight grade of venous stasis in the cerebral venous system. If the communication between the cerebral and the spinal venous systems is occluded (as was done by Hendrix in unpublished experiments made in the writer's laboratory), closure of the jugular veins causes as violent a dyspnea as that produced by occlusion of the carotid and vertebral arteries (Fig. 255). The rise in general venous pressure

which is an outstanding feature in congestive failure of the heart would inevitably be associated with some interference with the venous return from the central neurons, but whether the interference would be sufficient to warrant its being held responsible for some or all of the phenomena of cardiac dyspnea and orthopnea remains undetermined.

Another set of circumstances in which the cerebral circulation can be held responsible for dyspnea is found in *rise in cerebrospinal fluid pressure,* no matter how it is brought about. When this pressure becomes equal to that in the cerebral capillaries the flow of blood in the latter ceases; the effect is exerted equally throughout the cranial cavity because the container is indistensible

Fig. 255.—Dyspnea produced by interference with the venous return from the head.

Dog anesthetized with pentobarbital. Upper record—respiration (pneumograph); next record—femoral blood pressure. Vagodepressor nerves intact. The spinal venous sinuses were ligated from a ventral approach between the first and second cervical vertebrae; the vertebral arteries and veins were also ligated at the same level. Venous return from the brain was thus thrown largely if not entirely into the jugular veins. When these were clamped (between signals) respiration was stimulated (after a latent period of about 15 seconds), maximum increase being from 17 to 36 per minute. On release of veins blood pressure (which had been falling during the occlusion) rose sharply at once, fell, then rose again (probably because of changes in cardiac filling); there was an apnea about 15 seconds after the release, followed by gradual recovery. (From unpublished experiments by J. P. Hendrix.)

and the contents are incompressible. The medullary centers react to this acute anemia with hyperpnea and hypertension in the usual manner (Fig. 256); the vasomotor response leads to rise in pressure in the cerebral capillaries to the point at which the anemia is relieved, and this continues as the cerebrospinal

fluid pressure rises until the limit of the capacity of the vasomotor center has been reached; now acute anemia again ensues, but this time there is no longer any possibility of relief by further rise in blood pressure, and the central neurons rapidly fail (page 664). The breathing associated with increased intracranial tension is typically slow and labored (dyspneic), and it may be periodic (Fig. 257). It is not unlikely that an important factor in these respiratory and vasomotor responses is the onset of chemoreceptor reflexes aroused by anoxemia during the abnormally long period between breaths, the centers being so deranged by anoxia that they are no longer normally sensitive to changes in the CO_2 tension of their own environment; the breath (or group of breaths) removes the anoxic stimulus to the chemoreceptors and breathing ceases until anoxemia again supervenes.

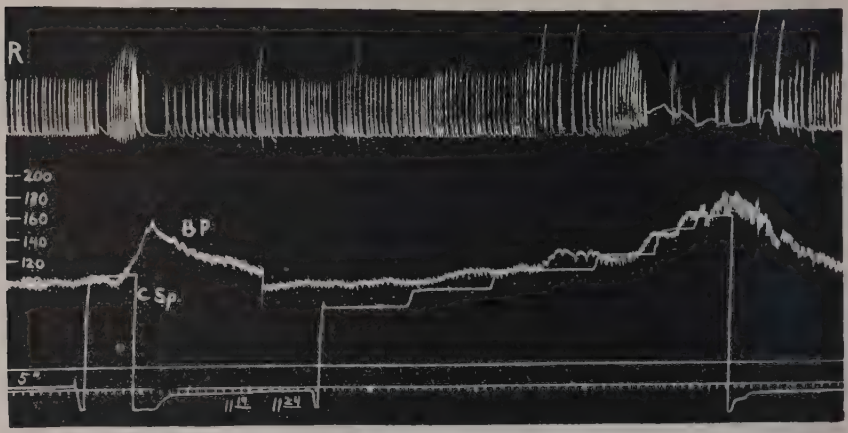


Fig. 256.—Effects of increased intracranial tension on blood pressure and respiration.

Dog anesthetized with barbital; all nerves intact; needle in cisterna magna connected through a warming coil to reservoir of saline solution that could be raised and lowered as desired. Respiration by pneumograph; blood pressure (from femoral artery) and pressure of fluid in cisterna both recorded by mercury manometers with time tracing (5-second intervals) as base line.

At left: sudden rapid elevation of cerebrospinal pressure (*C.Sp.*) to a level higher than arterial blood pressure (*BP*) evokes hyperpnea and hypertension.

Then cerebrospinal pressure was raised in steps, blood pressure rising with it and respiration showing stimulation until intracranial tension has risen to about 150 mm. Hg, when respiration ceases (except for a few feeble gasps); vasomotor center evidently was more resistant than respiratory center.

This brings us to the question of *periodic breathing* in general. The commonest form is Cheyne-Stokes respiration (Fig. 258), which is characterized by respiratory efforts that are at first weak but become successively stronger until definite dyspnea is present;[158] following this, breathing gradually diminishes until apnea occurs. It is noteworthy that the breathing, when it occurs, becomes dyspneic and for this reason we may consider the subject at this time.

The cyclic changes in respiratory activity are accompanied by changes in consciousness (which is clouded or absent during the apnea, improves as the breathing becomes more active, is nearest normal during the dyspnea, and fades as the breathing diminishes) and in blood pressure (which is usually though not always lowest at the time of apnea and highest during the dyspnea).

Cheyne-Stokes breathing is an ominous sign in disease, not because it is dangerous in itself, but because it is a signal of severe anoxia in the central nervous system. It is encountered in decompensated heart disease, in uremia, and in cases of disease or injury involving the brain. It may be seen in normal persons at high altitudes and has been described in aviators and mountain climbers, in the latter when asleep, in the former when they ascend rapidly and before consciousness is lost completely. Haldane and his collaborators[67] were able to produce it at will by subjecting themselves to anoxemia. It can also be produced in normal individuals by excessive overbreathing, as we have already seen (page 609). Finally, it is not uncommon in infants, especially in those born prematurely, and in these the apneic periods may be dangerously long.

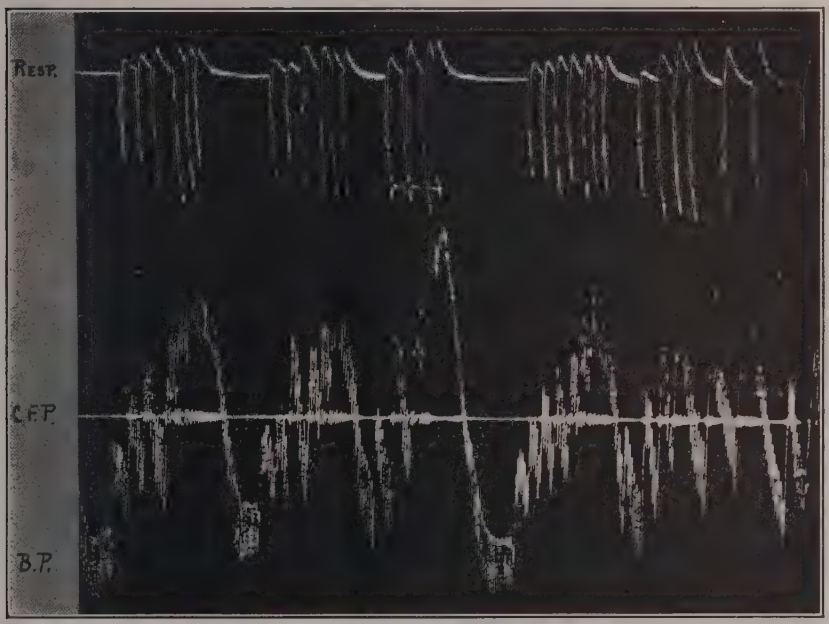


Fig. 257.—Periodic breathing due to increased intracranial pressure. Dog: arterial blood pressure (B.P.) and intracranial pressure (C.F.P.) recorded by mercury manometers set at same base line. Note breathing as arterial pressure rises above intracranial pressure, apnea as it falls below the latter. (From Eyster: J. Exp. Med. 8: 565, 1906.)

Cheyne-Stokes breathing is most probably due to anoxia in the brain in all cases; in newborn infants additional factors to be considered are injury during birth and congenital imperfection in the sensitivity of the respiratory neurons. The coincidence of improved consciousness with respiratory activity and of unconsciousness with apnea probably means that the entire brain undergoes the same rhythmic changes in capacity to function that are so evident in the respiratory center. The course of events is probably as follows: All nerve cells are depressed by anoxia; breathing stops, consciousness is lost, the vasomotor center loses its tone, and blood pressure falls. But the chemoreceptors can

still respond to the anoxemia and hypercapnia which result from the apnea; this, combined with the direct effect of the hypercapnia on the depressed but not paralyzed neurons of the center and the stimulus (reflex or direct) furnished by the fall in blood pressure, is enough to arouse the sluggish center and breathing begins. The blood is immediately oxygenated and the anoxic depression is quickly relieved: respiration improves, consciousness becomes less clouded, and blood pressure rises because the vasomotor center is now in better condition. But during the dyspnea the stimuli to chemoreceptors and center are reduced, breathing is depressed, and anoxia again supervenes.

In some patients, such as the one from whom the tracing shown in Fig. 258 was obtained, a prominent cause of the anoxia of the brain is spasm of cerebral blood vessels and breathing is made normal by drugs which dilate the vessels (theophylline, choline derivatives, nitrites). This is also the case in normal

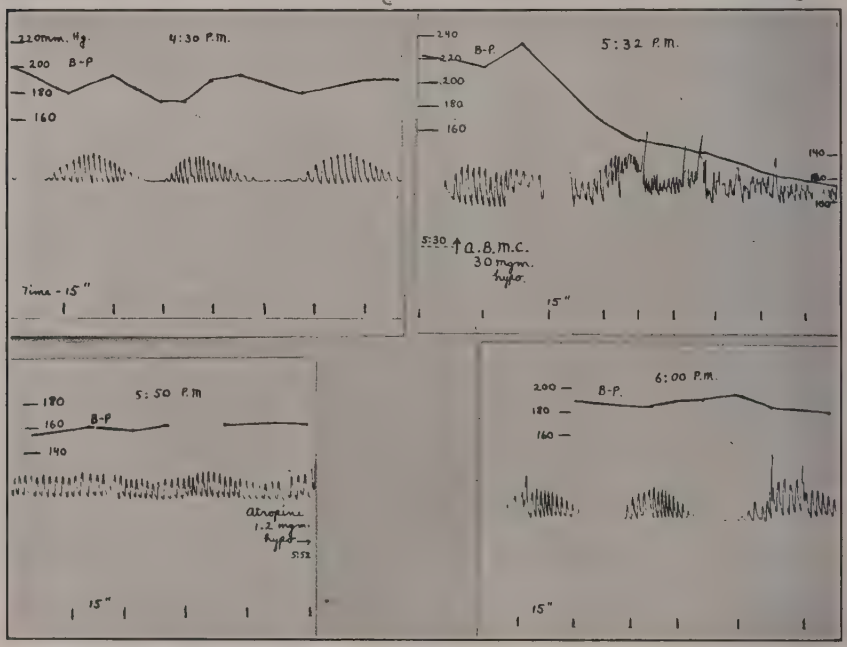


Fig. 258.—Cheyne-Stokes breathing in man.

Patient was seventy years of age, injured in trolley accident while under the influence of alcohol. No discernible damage to skull or brain. Record of respiration made by pneumograph; blood pressure read at frequent intervals by auscultatory method—systolic pressures drawn on record, calibration shown.

4:30 P.M.—control: patient completely unconscious during apneas, partly conscious while breathing. (He had been in this condition for more than twenty-four hours.)

5:30 P.M.—acetyl betamethylcholine—30 mg.—injected subcutaneously. Within a minute effects of drug began: face became flushed, there was profuse sweating, pulse became slower, and blood pressure fell from 220 to 118 (systolic) by 5:32. Patient became more nearly conscious than he had been for twenty-four hours: he tried to remove blood pressure cuff and struggled quite violently. Note absence of periodic breathing.

5:50 P.M.—patient asleep: no periodic breathing. Blood pressure has risen again as far as 155 mm.; skin still flushed and moist. At 5:52—atropine—1.2 mg. subcutaneously (to remove effects of the choline compound).

6:00 P.M.—atropine has acted: blood pressure has risen to 190 mm., skin pale. Periodic breathing has returned.

subjects who have developed Cheyne-Stokes breathing as a result of violent overventilation. In patients in whom cardiac disease is the cause oxygen inhalation quickly makes the breathing regular.

Cheyne-Stokes breathing due to high intracranial pressure resembles the form described above in that blood pressure typically rises during the dyspneic period and falls during the apnea (Fig. 257). There may be differences in the reactivity of the vasomotor and respiratory centers. If the vasomotor center is in better condition than the respiratory, blood pressure will rise before breathing begins because its cells are the first to respond to the rising stimuli, and the respiratory neurons are then helped by the improvement in their blood supply. In such cases respiration begins only after blood pressure has risen. But if the vasomotor neurons have suffered the same degree of damage as the respiratory, rise in blood pressure and onset of respiration coincide.

The ominous feature of Cheyne-Stokes breathing is that it indicates well-developed damage to the central nervous system by oxygen-lack. Breathing continues only because the respiratory neurons still have enough vitality left to respond to stimuli of abnormal strength, but they have lost their power to respond to slight changes and so to maintain normal breathing. The margin between damage severe enough to produce this condition and that sufficient to produce complete failure of breathing is probably very narrow.

(d) *Faulty Transport of the Respiratory Gases.*—This is responsible for the readiness with which dyspnea occurs in subjects whose alkali reserve is subnormal (acidosis, residence at high altitudes), or whose hemoglobin is subnormal in quantity (anemia) or quality (formation of compounds that do not yield oxygen with normal readiness, a result that can be brought about by carbon monoxide [carboxyhemoglobin—see page 694], and by substances which lead to the formation of methemoglobin or sulfhemoglobin). In many cases of this type dyspnea is not present under resting conditions because the existing circulatory and transport factors are adequate to supply the body's resting needs for a gas exchange and the chemoreceptors are not stimulated as long as the oxygen tension and pH in the arterial blood are normal (see page 592). Dyspnea does, however, occur with abnormal readiness when the metabolic needs of the body are increased.

The following generalizations, which are applicable to the phenomenon of dyspnea no matter how produced, may be of assistance to the physician in arriving at a decision as to what his attitude toward it should be:

1. Active contractions of the accessory inspiratory and the expiratory muscles account for a relatively excessive share of the total energy output of the body. This is indicated by Nielsen's work, to which allusion has been made (page 652). Since these muscle groups are necessarily involved in any dyspnea, it follows that dyspnea may be positively harmful as well as unpleasant to the patient, and it should be relieved whenever it is practicable to do so.

2. The subjective sensation of breathlessness appears always to depend upon persistence of the urge to breathe throughout the respiratory cycle, either because the combined nervous and chemical stimuli are overpoweringly strong or because the inhibito-inspiratory reflex influences are abnormally weak, or perhaps both. Direction of inquiry along these lines may lead to discovery of the responsible factor or factors and to proper decision as to how to remedy the situation.

3. There is a notable tendency to summation on the part of the various factors involved in dyspnea, and by far the commonest (and practically most important) instance of this is the well-known decreased tolerance to exercise. Present knowledge on this subject entitles us to conclude that there must be in such patients an abnormality which can stimulate the respiratory neurons either directly or reflexly but which is not yet severe enough to make itself manifest until the excitability of the center is increased by exercise. This factor may be one or more of those discussed above, and search along the proper lines may lead to its discovery in time to do something about it.

APNEA

Apnea simply means absence of breathing, but as generally used the term implies that the cessation is temporary. Prolonged apnea is simply respiratory failure and will be considered in the next section. Theoretically apnea might be produced by (1) reduction in the stimulus to the respiratory center, the latter having its normal ability to respond; (2) active inhibition of the discharge of impulses by the center, the stimulus being normal or augmented and the center likewise normal; (3) decrease in the ability of the center to react to the stimulus; (4) any combination of these. In experiments on anesthetized or decerebrate animals examples of the operation of each of these causes can be obtained without difficulty, and while the conditions are not actually normal, the underlying mechanisms are undoubtedly the same as in the normal animal.

Apnea in Experiments on Animals.—*Apnea due to reduction in the stimulus to the respiratory center* is seen when a reflex stimulus is suddenly withdrawn: the reduction in the chemical stimulus, which is produced by a hyperpnea of reflex origin, now makes itself manifest and breathing stops until the chemical stimulus is restored. A good example is the apnea which occurs when oxygen is breathed after inhalation of an indifferent gas such as nitrogen, hydrogen, or nitrous oxide (Fig. 259). A similar effect is produced by suddenly restoring the normal blood supply to the center during the stimulant stage of an acute cerebral anemia (Fig. 260). In this case the hyperpnea is due to accumulation of products of metabolism in the cells of the center, and the CO_2 tension of the blood is reduced; when the blood supply is restored, the diffusion of CO_2 takes place rapidly from the nerve cells to the blood, and apnea results until the CO_2 tension of the blood rises to normal again.*

Apnea due to active inhibition of the respiratory neurons can be produced by prolonging the inhibitory Hering-Breuer reflex, as by obstructing the trachea at the end of inspiration (Fig. 220, page 570). This causes relaxation of the inspiratory muscles and the resulting apnea lasts until the constantly rising CO_2 tension of the blood becomes stronger than the inhibitory nerve influence, for the latter diminishes only very slowly when the distention of the lungs remains constant (Adrian[2]).* A similar result is obtained when the carotid sinus pressure receptors are stimulated by a rise in intracarotid pressure (Fig. 226); the explanation is also similar, for the pressure receptors of the carotid sinuses, like the stretch receptors of the lungs, adapt very slowly (Bronk and Stella[31]) and the resumption of breathing is due to the overpowering effect of the increased chemical stimulus. In such cases the first respiratory effort is typically inspiratory, probably because the inspiratory neurons have a lower threshold than the expiratory to the CO_2 tension of the blood (page 556).

*Reflexes from the carotid sinuses play a part in the hyperpnea produced by occlusion of the carotid arteries and the apnea produced by release of the vessels, but they have little or nothing to do with the effects of simultaneous occlusion and release of the carotid and vertebral arteries, for denervation of the carotids does not modify the result. Adrenalin apnea (page 580) is also due in large part to reflexes from the circulation, but it can also be produced after section of the sinus and depressor nerves, in which case it is most probably due to decrease in the CO_2 tension in the respiratory neurons because of increased removal of the products of their own metabolism. As already mentioned (page 580) adrenalin apnea has little clinical importance because it is elicited only by intravenous injections of the drug and these produce such subjective disturbances in man that breathing is more likely to be stimulated than depressed.

Apnea due to decreased ability of the respiratory neurons to react to stimuli is produced by depressant drugs and poisons, especially when they are given so as to produce their effects very rapidly, as by intravenous injection. When so given most of these substances produce an immediate fall in blood pressure, before the central nervous effects are fully developed, and because of this (through reflexes from the carotid sinuses and aorta and through decreased removal of metabolic products from the center) breathing may be stimulated. By the time the central depressant effects have reached their maximum, the CO_2 tension of the blood may therefore be reduced by the initial hyperpnea and both influences combine to cause cessation of breathing. If the depression caused by the drug is not too severe breathing will begin

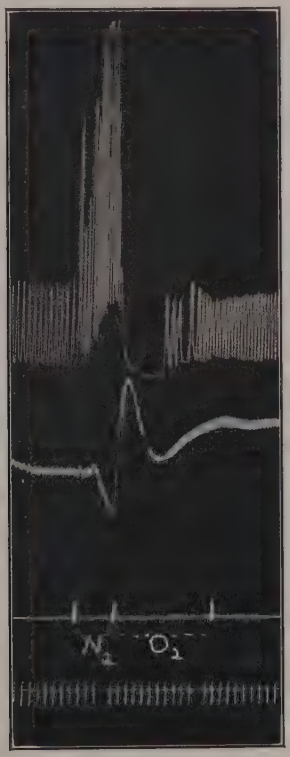


Fig. 259.

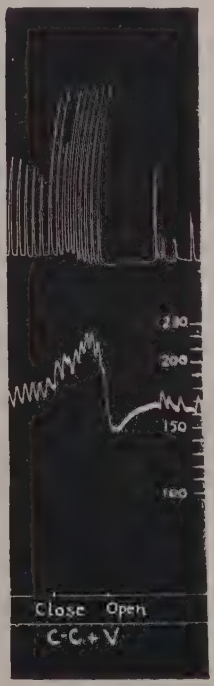


Fig. 260.

Fig. 259.—Apnea due to breathing oxygen after nitrogen. Cat—pentobarbital narcosis. Respiration recorded by plethysmograph, blood pressure by Hg manometer connected with femoral artery. Vagodepressor and sinus nerves intact. Nitrogen (undiluted) inhaled between first pair of signals. When dyspnea was at its height, nitrogen was removed and oxygen was supplied through a tracheal catheter until third signal mark. Time record shows five-second intervals.

Fig. 260.—Apnea due to restoration of blood supply of brain after a brief period of acute anemia. Dog: barbital narcosis; carotid sinuses denervated, vagodepressor nerves cut. Common carotid and vertebral arteries (C-C+V) closed and opened as indicated. Calibration at right applies to blood pressure record. (From Schmidt: Am. J. Physiol. **102**: 119, 1932.)

again when the CO_2 tension of the blood has risen sufficiently to arouse the now sluggish neurons to activity (Fig. 261). In all such cases the CO_2 tension of the blood rises above normal and the extent of the rise is a fair measure of the extent to which the reactivity of the neurons has been reduced.

Combinations of these are frequently encountered. The commonest and most important one is *simultaneous reduction in the stimulus and in the ability of the center to react to it.* This has just been mentioned in connection with intravenous injection of narcotic substances. It has also been mentioned (page 600) as a danger in inhalation anesthesia. A similar combination is encountered in *anoxemia* or in *oxygen-lack in the central neurons due to cerebral anemia no matter how produced,* for in anoxemia breathing is driven by reflexes and in cerebral anemia by accumulation of metabolic products in the cells of the center; the normal stimulus (blood CO_2) is reduced by the hyperpnea and the ability of the cells to react is simultaneously reduced by oxygen-lack within them. *Active inhibition of the cells of the center* becomes a serious factor only when it is combined with a diminution in the reactivity of the cells to chemical influences while their reactivity to afferent inhibitory influences is less reduced or actually exaggerated. This is the situation in animals anesthetized with chloralose, to a lesser extent after large doses of morphine; it also seems to be the case in some animals (and human subjects) under anesthesia by nitrous oxide and oxygen (Downs[48]).

Apnea in Man.*—All the types of apnea which we have just seen illustrated in experiments on anesthetized or decerebrate animals have their counterpart in man. The apnea due to reduction in the stimulus to the respiratory center is shown by overbreathing voluntarily for about two minutes, after which the subject has no desire to breathe again until the CO_2 tension of the blood has returned to normal. The apnea due to active inhibition

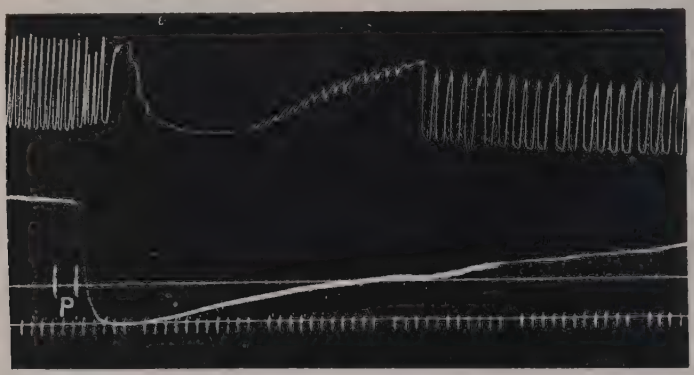


Fig. 261.—Apnea due to depression of the respiratory center by a depressant drug injected intravenously. Cat under light pentobarbital narcosis (corneal reflex active). At *P*, intravenous injection of 60 mg. of pentobarbital sodium.

of the respiratory neurons is illustrated by holding the breath voluntarily. Both of these types of apnea can be elicited more readily in normal man than in animals, not only because of voluntary cooperation, but also because the respiratory neurons are in a state of maximal reactivity to stimuli of all sorts. The apneas which depend on decreased reactivity of the center are also encountered in man—those produced by sudden absorption of a depressant drug as well as those due to oxygen-lack within the cells of the center. The latter frequently take the form of periodic respiration in man, which has already been considered (page 656).

RESPIRATORY FAILURE

Up to this point we have generally assumed that the sensitivity of the respiratory neurons is always the same and that differences in breathing are due to differences in the intensity of the chemical or nervous influences which act

*Until about five years ago it was generally believed that apnea normally exists in the fetus in utero and physiologists attempted to explain in various ways the beginning of respiration after birth. The work of Snyder and Rosenfeld, shows clearly that respiration is normally present in the fetus before birth; the first breath of air is simply a continuation of a process which has been going on for some time and which has been interrupted or impeded by the process of labor.

upon the center. In terms of the conception outlined on page 562, this means that the vegetative reactions of the neurons are being perfectly carried out and the capacity for generating and discharging motor impulses is maximal. It is under such circumstances that the respiratory center is so exceedingly sensitive to changes in the CO_2 tension of the blood. If all other factors are kept constant, the same maximal sensitivity to CO_2 is expressed in constancy of the CO_2 tension of the alveolar air.

These are ideal conditions for demonstrating the reactivity of the respiratory center, and it would be a mistake to apply the information so obtained to the abnormal situations which confront the physician; first some assurance should be had that the reactions of the respiratory center damaged by trauma, poisons, or disease are at least qualitatively like those of the normal. As a matter of fact they are not; the response of the center when it is depressed is not only quantitatively reduced but it is in some respects exactly opposite to the response under normal conditions. Since the physician's concern with the respiratory center is mainly limited to the abnormal, it is important to understand these differences.

The respiratory center is a relatively rugged structure. It has greater capacity to resist adverse conditions without surrendering its functions than any other part of the central nervous system excepting the closely related vasomotor center. This is seen in the familiar fact of general anesthesia, which is possible only because the respiratory and vasomotor neurons are able to continue at least a passable semblance of their normal activities when subjected to poisoning of a degree sufficient to paralyze the rest of the central nervous axis. It is also seen in the fact that respiratory and vasomotor functions can be restored even as long as 30 minutes after the circulation has ceased,[41] whereas the higher, more complexly organized parts of the central nervous system are irreparably damaged. The desire to breathe is perhaps the most irresistible of all the activities of the mammalian central nervous system. It is said[89] that man succumbs to immersion in water considerably sooner than necessary because he is unable to resist the impulse to breathe; consequently he draws water into his lungs and displaces the reserve supply of air in them long before he has utilized the oxygen which it contains. Recent studies[86, 95] of the factors responsible for the ability of diving mammals to remain submerged for relatively long periods of time make it probable that one of the most important of these factors is the ability to suppress the desire to breathe when it can only do harm to the organism. A similar ability is very seldom if ever sufficiently developed in normal man to permit us to regard inhibition of the normal human respiratory center as a possible cause of a dangerously long suspension of respiratory activity. Such a contingency can be expected only when the neurons are no longer normal.

It is obvious that the respiratory center cannot always have the same ability to react to stimuli. No matter how great its capacity for discharging impulses may be when its neurons are in a state of maximal reactivity, and no matter how much more resistant it is to adverse conditions than the rest of the central nervous system, its activity must eventually be decreased by the same agencies which decrease the activity of all living cells. This is indeed the case.

Severe asphyxia or anoxemia no matter how produced (pages 649 and 675) will eventually lead to cessation of breathing; respiration typically stops before the heart ceases to beat and the failure of the circulation is properly regarded as secondary to the failure of respiration. Among the commonest (and least hopeless) causes of this type of respiratory failure are inhalation of asphyxiating gases, drowning, practically total obstruction to the passage of air in and out of the lungs, and failure of the respiratory muscles (as in excessively high spinal anesthesia, transverse cord lesions, poliomyelitis, or extreme myasthenia). Respiratory and cardiac failure also ensue inevitably whenever the circulation fails because the flow of blood then becomes inadequate to supply enough oxygen to prevent anoxic derangement of the cells of the respiratory center and heart muscle; in such cases the restoration of these functions is impossible unless or until the circulation is restored.

The respiratory neurons are depressed by narcotic drugs such as alcohol, ether, chloroform, morphine, the barbiturates, and other depressants of the central nervous system. In

line with current trends we may attribute this depression in reactivity to an interference by the narcotic with the vegetative reactions of the neurons, thus leading to an increase in the interval required for them to prepare for another burst of activity (slowing in the rate of breathing) and to a decrease in the number of neurons involved in each burst (decrease in the depth) (see page 562). If the drugs are present in sufficient amounts, the nerve cells are rendered completely incapable of reacting to stimuli and respiration ceases. Usually the poisoning develops gradually as the concentration of the drug in the tissues increases and respiration becomes progressively slower and usually shallower before it fails entirely. Before the neurons are completely paralyzed, they can still react to increased stimuli, nervous or chemical, although much more sluggishly and much less strikingly than normally. Even after they have ceased functioning, they may still be aroused if the nervous or chemical stimuli which affect them are further increased. It is noteworthy, however, that the oxygen requirement of these neurons is reduced by narcosis and their susceptibility to the disorganizing effects of anoxia is correspondingly diminished—a relation of some importance in connection with resuscitation.

In addition to narcotic drugs, there are poisons which act primarily by interfering with tissue oxidations and which depress breathing because the respiratory neurons, like any other living cells, are depressed when their oxidative processes are deranged. The outstanding examples are carbon monoxide and cyanide. Monoxide acts by forming a stable compound with hemoglobin and thus preventing the liberation of oxygen from it (see page 692). Cyanide prevents the cells from utilizing oxygen (see page 714). Either may cause stimulation of breathing at first, but the serious aspect of their action is the respiratory depression which ensues.

Respiratory depression or failure is also a prominent danger in injury to the central nervous system. When the damage involves the medulla, through direct trauma or hemorrhage extending into it, the mechanism is quite evident, but the danger exists even when the medulla is not directly injured. This is because cerebrospinal pressure is likely to be elevated; when this pressure exceeds that in the cerebral capillaries the flow of blood in the latter becomes impossible and the entire brain suffers from acute anemia (see page 655). Cerebrospinal pressure is raised in inflammatory disease and tumors of the central nervous system and in certain toxemias, such as uremia and eclampsia, which do not involve the central nervous system directly. In narcotic poisoning the cerebrospinal pressure is usually elevated also —a fact which may be of importance in determining the outcome, for in such cases the vasomotor center is much less reactive than normally and therefore incapable of raising the blood pressure as it should.

Respiration is also depressed by anemia of the brain produced by mechanisms other than increased cerebrospinal pressure. This is apt to be forgotten because acute cerebral anemia produces a marked stimulation of breathing if the center is normal (page 653). This stimulation is transitory; if the anemia continues, the respiratory stimulant response is not maintained, but gives way either to a return to normal breathing or to progressive depression followed by failure. Such a situation is encountered whenever the blood pressure is markedly reduced, as in hemorrhage or shock. A reduction in cerebral blood flow that would be unimportant under ordinary circumstances may cause respiratory failure if produced when the supply of oxygen to the brain is deficient because of a shortage either in the oxygen content of the blood or in the amount of blood flowing through the organ. This probably accounts for permanent respiratory failure on stimulation of the carotid sinus pressoreceptors during nitrous oxide anesthesia (Downs[48]) and perhaps also for the tendency of patients with high cerebrospinal pressures to cease breathing when relatively slight reductions in blood pressure are brought about.

Respiratory failure may occasionally follow the sudden relief of a sub-total obstruction of the respiratory tract when performed during the dyspneic stage, as by intubation of the larynx, or by insertion of a tracheotomy tube in a patient with laryngeal obstruction.[117] The mechanisms involved here are as yet very imperfectly understood. The explanation that seems most probable to the writer is that the central neurons had previously suffered so much damage from prolonged exposure to anoxemia that they could be kept active only by a powerful chemoreceptor drive (also due to anoxemia), and when the latter is suddenly eliminated by the first free breath or two after the operation, the neurons cease functioning. Perhaps the situation here is essentially the same as that described by Courville[42] in connection with delayed deaths or permanent neurologic sequelae following

nitrous oxide anesthesia, viz., more or less extensive degenerative lesions in the brain substance itself—a situation that can be prevented but not remedied.

A special form of respiratory failure is that encountered in newborn infants. This will be dealt with separately (page 672).

These are circumstances under which depression or failure of respiration is likely to cause death and improvement of respiration may lead to recovery. This is especially true in poisoning by depressant drugs, for these do not directly damage the tissues. There is one common factor in all of the conditions in which respiratory failure is likely to occur, and that is oxygen-lack in the cells of the center. In narcotic poisoning it is produced by the decreased pulmonary ventila-

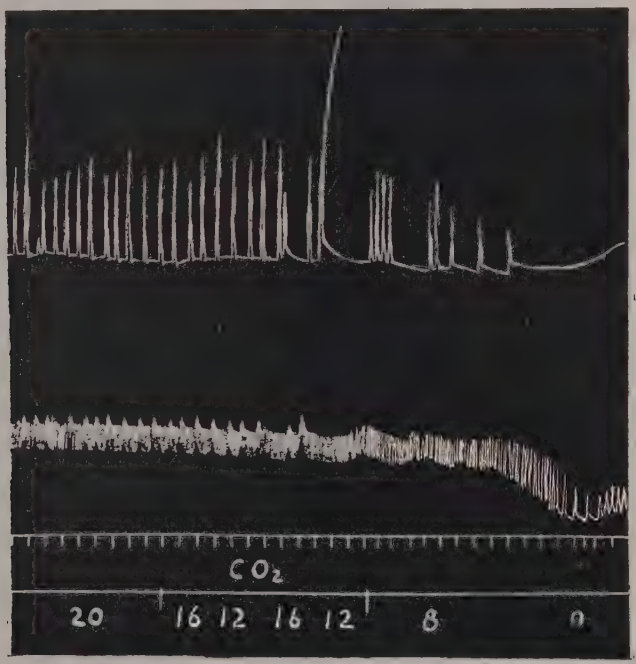


Fig. 262.—Respiratory failure following inhalation of CO_2. Dog: urethane and morphine. CO_2—6 per cent in air—inhaled for one minute; the numbers indicate rate of respiration per minute. Upper record, respiration; lower record, arterial pressure. (From Schmidt: Am. J. Physiol. 84: 202, 1928.)

tion consequent upon the narcotic depression of the center; by an interference by the narcotics with cell oxidations including those in the respiratory neurons; by depression of the vasomotor center, an effect which all these substances are likely to have in toxic dosage; and by the raised cerebrospinal pressure which is also commonly produced by them when the dosage is dangerously large. In poisoning by carbon monoxide or cyanide the oxygen shortage is begun by deficient supply of oxygen by the blood (monoxide) or by deficient utilization of oxygen by the cells of the center (cyanide), but as respiration becomes depressed, insufficient pulmonary ventilation adds another factor leading to oxygen-

lack; in addition, cerebrospinal pressure is raised in monoxide poisoning. In cases of subacute cerebral anemia, whether due to high intracranial pressure or to low systemic blood pressure, the chief factor is an insufficient supply of blood to the center: it does not get enough food material or oxygen and its waste products accumulate within it.

In all these cases the respiratory center suffers from shortage of oxygen and since this can be remedied promptly while relief of direct depression of the center by trauma or poisoning requires time, it is important to recognize the dangers of oxygen-lack and to remove them as far as possible. Shortage of oxygen is not narcotic in the usual sense but rather disorganizes the internal economy of the cells. It reduces specialized functions because it interferes with the vegetative reactions upon which the specialized functions are based (p. 519).

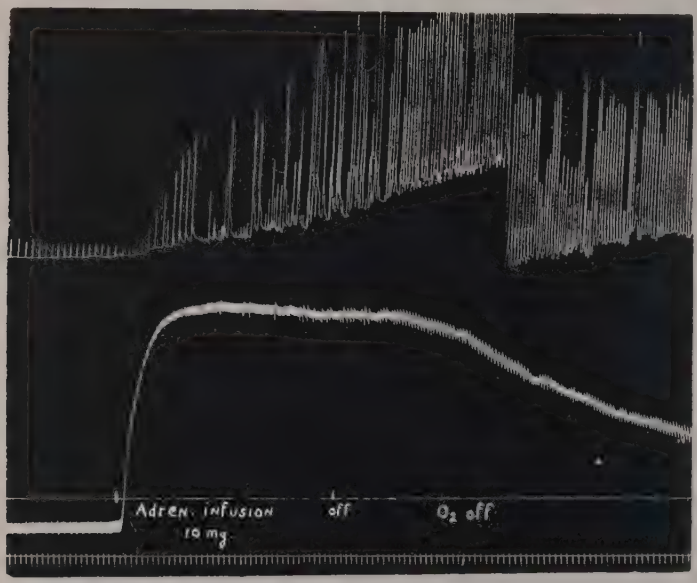


Fig. 263.—Respiratory stimulation by adrenalin. Dog: urethane and morphine. Upper record respiration; lower, arterial blood pressure. Oxygen by catheter in trachea for five minutes before this record was made—discontinued at "O_2 off."

This sort of change is added to that which had caused the initial depression of respiration and a vicious circle is set up: oxygen-lack in the neurons leads to further respiratory depression, this leads to further diminution in the amount of oxygen taken into the blood, and this causes still further depression of the center. The depression originally caused by trauma or poison is thus intensified.

Under such circumstances the behavior of the respiratory center differs both quantitatively and qualitatively from the normal. Quantitatively, the response to chemical stimuli is greatly reduced, as one would expect, since breathing is depressed although the CO_2 tension of the blood is abnormally high; CO_2 inhalation may elicit some stimulant response but this is apt to be slight at best, and it may be entirely lacking. Afferent stimuli, particularly those arising from the chemoreceptors, are relatively more important than they are normally, and breathing may be maintained only because anoxemia is present, the center having lost practi-

cally all of its normal capacity for responding to changes in carbon dioxide content in its cells, while the receptors of the carotid and aortic bodies continue to function. Consequently, substances which normally excite these receptors (such as lobeline and cyanide) are usually more effective than CO_2 inhalation in stimulating breathing when it is about to fail or has failed, but the effects are much less intense than they normally are and when breathing has ceased these agents may be entirely ineffective. Drugs which arouse nerve cells to greater activity (strychnine, caffeine, atropine, camphor, picrotoxin, metrazol, coramine) produce progressively less respiratory stimulation as the depression becomes more profound, and when death is imminent, because of insufficient respiration, they are apt to be entirely ineffective.

As for *qualitative* differences from normal, the respiratory center that has been subjected to oxygen-lack for some time may be depressed by agents which normally stimulate breathing and it may be stimulated by agents which normally would depress it. Thus CO_2 inhalation, or any of the drugs which stimulate nerve cells, may cause brief stimulation followed by depression or failure of breathing (Fig. 262), while adrenalin, which normally causes apnea, is one of the most effective agents in restoring breathing after it has failed (Fig. 263).

The explanation of this paradox is probably as follows: when the central neurons are laboring under a supply of oxygen barely sufficient to meet their needs, a stimulation of their activity entails an increased call for oxygen which cannot be furnished, and a subacute oxygen shortage is thus transformed into an acute one—hence the transitory stimulation followed by depression. On the other hand, the increase in blood pressure produced by adrenalin greatly increases the blood supply of the brain; normally this means inhibition of respiration through stimulation of the pressure receptors of the carotid sinus and aortic systems as well as removal of stimulant material produced in the center by its own metabolism, but now the increased blood supply of the center increases the amount of oxygen available to it and at the same time washes depressant material (accumulated metabolic products, narcotic drugs if present) out of it; thus its capacity for discharging impulses is increased.

From these considerations it follows that respiratory failure, for all practical purposes, may be regarded as synonymous with severe anoxia in the neurons of the respiratory center. In most cases anoxia plays a prominent part in bringing about the initial failure by disorganizing these cells and diminishing their capacity to respond to stimuli, but even if this were not the case anoxia would inevitably result as soon as the breathing became insufficient. This conclusion is of the utmost importance when it comes to restoring breathing after it has failed, which is the subject next to be considered.

RESUSCITATION

Having considered the conditions under which respiratory failure may occur and the underlying derangements in the regulating system, we come to an inquiry into the measures that should be employed to rectify these disturbances and thus to restore respiratory activity. If we are correct in our conclusion that disorganization of the central neurons by anoxia is a common factor of dominant importance in all cases of respiratory failure, several deductions of importance with regard to the physician's attitude toward these conditions may at once be drawn: (1) *Prevention is greatly to be preferred to cure,* for anoxia is prone to set vicious circles into operation and to cause irreversible changes in the central nervous system (Chapter XLV); the margin between complete reversibility (i.e., full recovery) and partial (i.e., permanent neurological sequelae) or complete irreversibility (i.e., failure to reinstate any vital activity) must be narrow at best, variable, and unpredictable. (2) *Speed is essential,* for the ability of the cortical cells concerned with the higher cerebral functions to withstand the disintegrative influence of anoxia is much less than that of the medullary neurons, and even though it is possible to restore respiratory activity as long as thirty minutes after the heart has ceased to beat[41] the cerebral functions of such an individual are not likely to return. (3) *No good will be accomplished by inducing greater activity in the central neurons unless their functional state is improved at the same time;* on the contrary, as we have just seen, attempts at resuscitation that involve increased activity by the neurons when their oxygen supply is barely adequate may turn a subacute oxygen shortage into an acute one and thus lead to complete failure. (4) *Successful resuscitation after respiration has failed must always depend upon two things:* (a) *improvement in the capacity of the neurons of the center for carrying on their function, which means rectification of the disorganizing effects of anoxia, removal of depressant poisons if present and avoidance of reduction in the carbon dioxide tension of the blood to a level below that required to maintain activity*

in the respiratory neurons (page 672); (b) *prevention of further (probably irretrievable) damage by anoxia during (or because of) the attempt at restoration.*

If these general principles are valid (as I believe them to be), it follows that the physician's attention in all cases in which resuscitation is attempted should be focused upon the institution and maintenance of an adequate supply of oxygen to the brain and the heart, for these are not only the parts of the body upon which resuscitation most directly depends but they are also the most vulnerable of all body tissues to the disorganizing effects of oxygen lack. If an abundant supply of oxygen is provided for these structures recovery will take care of itself; if it is not recovery is manifestly impossible.

From this viewpoint the appropriate procedures are as follows:

(1) *Provision must first be made for securing an adequate oxygenation of the blood in the lungs* and the first step is to see that the air-bearing system is freed of obstructions by appropriate measures (removal of water in drowning, in other cases by intubation of the larynx, tracheotomy, removal of foreign bodies, etc.). Then oxygen (if available) should be administered (preferably with the addition of about 5 per cent CO_2—see below), either through a suitable inhalator or by means of a catheter passed down the trachea to its

Fig. 264.—Resuscitation by oxygen administered by tracheal catheter. Cat: pentobarbital narcosis; at P—pentobarbital sodium—130 mg.—injected intravenously; oxygen administered by catheter between signals at "Oxygen." Note restoration of blood pressure and respiration by this procedure, indicating that oxygen-lack (produced by the initial cessation of breathing) was responsible for much of the total depression.

bifurcation (Figs. 264 and 265). Artificial respiration may also be applied, but the temptation to overdo this (which is great) should be resisted if oxygen is being supplied by the tracheal catheter, for the alveolar gas pressure may then be raised sufficiently to interfere with the pulmonary circulation. Once the oxygenation of blood in the lungs has been cared for, if the heart is still beating there is no danger of immediate death and the remaining measures can be applied deliberately. If the heart is no longer beating, immediate steps (such as intracardiac injection of adrenalin plus cardiac massage) must be taken to start it; this should not be done before oxygenation of the blood in the lungs has been cared for because, if it is, the increased cardiac effort resulting from adrenalin (if effective) will probably lead to rapid and irretrievable cardiac failure unless the blood in the coronary arteries is well oxygenated.

(2) *Attention should now be directed to the circulation,* for it is by this, and this alone, that oxygen is carried to the brain and depressant poisons (metabolic products or foreign chemicals) are removed from it. If blood pressure is low, steps should be taken to raise it (by transfusion of blood or by pressor drugs such as adrenalin, ephedrine, benzedrine, paredrine, etc., see Figs. 263 and 266). If the pressure of the cerebrospinal fluid is high, it may

be lowered by the intravenous administration of hypertonic fluids (sucrose or d-sorbitol in 50 per cent solution, or concentrated "lyophile" serum*); since anoxia apparently produces a distinct increase in the permeability of cerebral blood vessels, the administration of large amounts of fluid in such cases is undesirable because of the likelihood of further cerebral edema and a further rise in cerebrospinal pressure; the advisability of lowering this pressure by removal of fluid in the lumbar or cisternal space calls for clinical judgment; the physician must remember that if the cerebrospinal pressure is as high as or higher than that in the cerebral capillaries (which must be at least a little lower than that in the major arteries) resuscitation is impossible. The observer must be prepared for a rapid and steady decline of blood pressure if adrenalin has been used to start the heart or to raise the blood pressure, for this drug is rapidly destroyed in the body and its effects are correspondingly brief. Furthermore, oxygen inhalation or insufflation may cause a fall in blood pressure

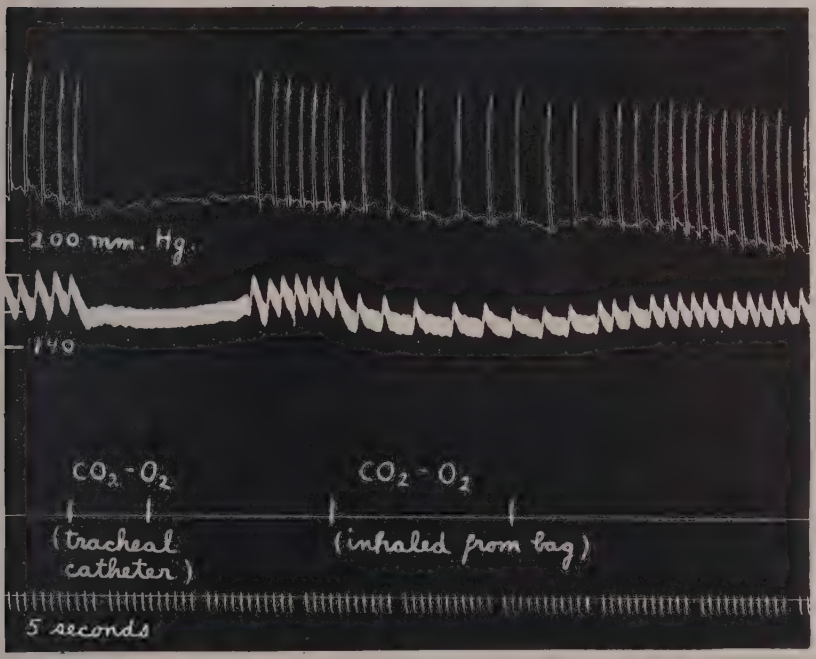


Fig. 265.—Depression or cessation of respiration as a result of inhalation of CO_2 and O_2.

Dog: anesthesia by urethane and chloralose. Vagodepressor and sinus nerves intact. Upper record—pneumogram. Femoral blood pressure—mercury manometer, calibration shown.

CO_2—10 per cent in oxygen—administered first by catheter whose tip lay just above bifurcation of trachea, then by inhalation from a bag attached to inspiratory valve of tracheal cannula.

Depression of breathing was probably due to removal of anoxemia.

in certain instances, probably because impulses aroused in the chemoreceptors by anoxemia have been instrumental in maintaining vasomotor activity (the so-called MacDowall reflex—Comroe[39]). Care should be taken lest the preoccupation of the observer with other matters

*These are better than glucose because the latter, being so much more readily diffusible through living membranes, is apt to leave the circulation and enter the brain where it will attract more fluid and may cause a rise in intracranial pressure to a level higher than the initial one. The saccharides have the advantage, in cases of narcotic poisoning, of causing considerable diuresis, which aids in the removal of the toxic agent from the body after it has been detached from the brain cells and before it can recombine with them. Sucrose has recently[100] been accused of causing severe damage to the kidney, and perhaps sorbitol, which seems above suspicion in this regard, deserves preference.

lead him to neglect these phenomena until the circulation has become insufficient. The patient's body temperature should also be watched and steps taken to see that it does not fall, as it may; in poisoning by barbiturates, however, fever is not unusual.

(3) *Steps may now be taken to remove the cause of the original depression.* If this was largely or wholly due to the disorganizing effects of anoxia, nothing need (or can) be done other than to insure an adequate oxygenation of the blood in the lungs, an adequate flow of blood in the cerebral and coronary systems (both dependent directly on the level of systolic blood pressure), and an adequate content of carbon dioxide in the arterial blood; since carbon dioxide is also a most effective dilator of cerebral vessels, an adequate patency of these is thus insured without the risk of additional cerebral edema or fall in systemic blood pressure that would attend the use of vasodilator drugs other than CO_2. The use of stimulant drugs, in hopes of hastening the return of spontaneous breathing, is probably advisable only if depressant drugs were a factor in the original depression. When the depression was due to a drug or poison, specific measures aimed at getting rid of the toxic agent will be indicated, but these will vary according to the substance to be removed: in poisoning by carbon monoxide, inhalation of oxygen plus carbon dioxide is effective (page 694); in cyanide poisoning the administration of nitrites and sodium thiosulfate leads to the

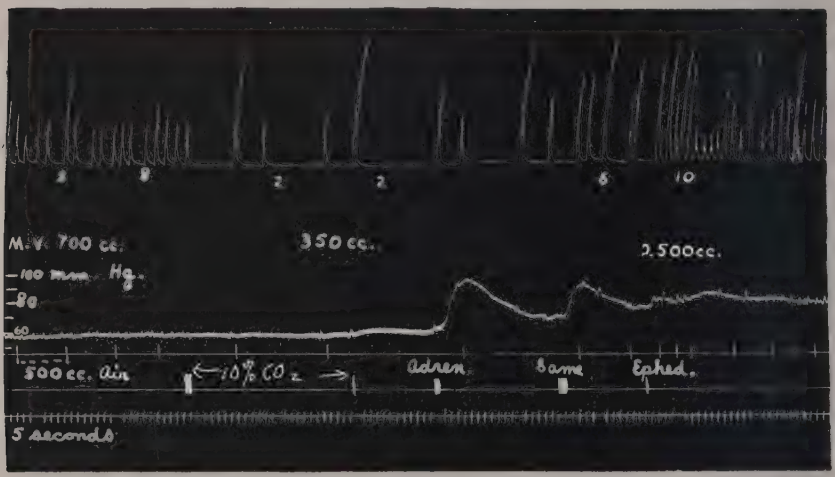


Fig. 266.—Further depression of a depressed respiratory center by inhalation of CO_2 in O_2

Dog: anesthesia by urethane and chloralose; 100 mg. of morphine sulfate injected intravenously ten minutes previously. Vagodepressor and sinus nerves intact. Records (from above down): respiratory movements (pneumogram), rate indicated; femoral blood pressure—mercury manometer, zero at time tracing, calibration shown; volume of expired air, each signal mark repesenting 500 c.c. (ml.), minute volume (*M-V*) shown under figures for respiratory rate; signal; time.

CO_2—10 per cent in oxygen—administered from bag through inspiratory valve attached to tracheal cannula.

Adren.—adrenalin—0.5 mg.—intravenously.

Ephed.—ephedrine hydrochloride—10 mg.—intravenously.

Depression of breathing followed two breaths of the CO_2–O_2 mixture and was probably due to the narcotic effects of CO_2. Note improvement following adrenalin and ephedrine.

formation of cyanhemoglobin and the transformation of the cyanide into relatively harmless thiocyanate; in poisoning by narcotics, or other agents taken by mouth, lavage of the stomach and the administration of activated charcoal (to adsorb the remaining poison) and of dilute sodium (not magnesium, which is itself a narcotic) sulfate or phosphate, to hasten this along the bowel, are measures to be employed. In narcotic poisoning it is also to be remembered that removal of the poison from the brain must be accomplished by the circulation, and, other things being equal, the better the circulation the more rapid the recovery.

The question of *respiratory stimulant (analeptic) drugs* has intentionally been put last in this discussion because (in my opinion) their value is considerably smaller than their potentialities for doing harm. Our inquiry into the derangements that must be remedied or compensated if resuscitation is to be successful should have disclosed the futility of the search for a *therapia magna*—a specific, multivalent remedy—for all forms of respiratory failure. By this time it should be clear that there is need for rapid, effective action whenever anoxia is at work if irretrievable damage is to be avoided, and the precious time used in administering one or more of the analeptic drugs (strychnine, camphor, atropine, caffeine, picrotoxin, metrazol, coramine, hexeton, etc.), and in waiting for their effects to appear, may be very badly spent. It would seem to be better on the whole for the physician to forget all about these drugs under such circumstances and to concentrate his attention on measures that can be counted upon to break the vicious circle of anoxia, as encountered when respiration has become inadequate. These measures have already been considered (page 668).* Most of the drugs by which respiratory failure is apt to be produced have relatively prolonged effects and most of them are excreted unchanged from the body to a greater or lesser extent. Even if the analeptic succeeds in dislodging such a drug from combination with the neurons the depressant may recombine as soon as the effects of the analeptic wear away. Thus it would be unusual for any analeptic (or combination of analeptics), unsupported by other measures, to furnish an adequate treatment in narcotic poisoning sufficiently severe for the treatment to determine the outcome, even when the depression is almost purely a phenomenon of narcotic poisoning with a minimum of complication by anoxic derangement of the neurons. Since the narcotic depression is a completely reversible process, recovery should result just as surely, if perhaps a little more slowly, without the analeptic, simply from maintaining a good oxygenation of the blood in the lungs and a good circulation through the brain and heart. The latter, in my opinion, is the preferable procedure because of greater certainty in terminating and obviating anoxia and smaller risk of doing harm, either through self-deception or through aggravation of the anoxia. The depression due to anoxia cannot be favorably influenced by an analeptic and may be made worse.†

From the standpoint of effectiveness in eliciting respiratory movements the drugs which stimulate the chemoreceptors (lobeline and cyanide are the only ones that have been used therapeutically) are undoubtedly superior to the analeptics or convulsants. This is probably because the respiratory neurons, whenever resuscitation is needed, have been so deranged that they have lost the ability to respond to changes in the chemical composition of their environment and this derangement cannot readily be rectified by a convulsant drug; at the same time they may still be able to respond to the (presumably) more violent reflex disturbance set up in their vicinity by maximal stimulation of the chemoreceptors (see page 592). It should be noted, however, that the strong chemoreceptor stimulants are (as far as is now known) depressant to nerve cell activity, and reflex stimulation of respiration by them is therefore accomplished at the risk of further depression of the central neurons, not only because an existing derangement is apt to be intensified by increased activity thus demanded of them under adverse circumstances, but also because the agent responsible for the increased activity may directly add to the derangement. The place of such stimulants in the picture of resuscitation would seem to be to serve as tests of the possibility of resuscitation when respiration does not begin even though the oxygen and carbon dioxide

*The analeptics probably have a real place in the treatment of very acute overdosage with narcotic drugs; perhaps the best possible place for them is found in the recent practice of continuous intravenous infusion of a rapidly acting barbiturate such as pentothal. Under such circumstances the excessive depression occurs under the eyes of the anesthetist, is immediately recognized, and can promptly be remedied by intravenous injection of an analeptic (picrotoxin seems most successful). The action here is probably a displacement of the narcotic from its anchorage in the nerve cells by means of the analeptic, and a component of anoxic depression is minimal, partly because this type of anesthetic procedure is (it is to be hoped) carried out only by skilled individuals provided with all the necessary equipment, partly because the demand of the brain cells for oxygen is reduced by the depressant drug as the narcosis deepens. It should be noted, however, that the only narcotics that can be used in this way without undue risk have very brief effects; they are not likely to recombine with nerve cells after they have been detached and the original depression therefore should not return subsequently. A similarly ideal set of indications for an analeptic is probably not to be expected under any other circumstances: the onset of respiratory failure under the eyes of a specially skilled attendant who is looking for it and is prepared to take appropriate action instantly without permitting anoxia to supervene, the depression brought about by a drug the effects of which are very brief—each of these is distinctly unusual and seldom encountered, and the coincidence is probably unique. Narcotic poisonings as a rule develop gradually and by the time breathing has failed circulatory depression and anoxemia will have existed for some time.

†The cause of death in many cases of barbiturate poisoning in man is not respiratory depression but intercurrent pulmonary infection. This is another reason for concluding that the value of analeptics in such conditions is very limited if existent.

content of the arterial blood and the blood supply of the brain and heart have been cared for. These drugs cannot safely be used to maintain breathing under such circumstances, since the margin between reflex stimulation and direct central depression is entirely uncertain; they certainly cannot be used to replace the other procedures and they lack the property (possessed by the analeptics) of displacing narcotic drugs from combination with nerve cells.

THE EFFECTS OF INHALATION OF CO_2 IN OXYGEN WHEN THE RESPIRATORY CENTER IS SEVERELY DEPRESSED

These merit special attention because inhalation of CO_2 has come into widespread use for resuscitation. The general belief is that it is the most effective means of stimulating a depressed or paralyzed respiratory center and that even if it does no good it can do no harm. We must remember, however, that CO_2 is not a general stimulant to nerve cell activity, but is a depressant (narcotic) in the same sense, and probably through the same mechanisms, as alcohol or ether (Winterstein[151]). Its stimulant effects upon the medullary centers are quite unusual, and must be regarded as the result of a highly specialized function of these cells. But specialized functions are readily deranged, and this one certainly is deranged when respiration is badly depressed or ceases in the face of an abnormally high CO_2 tension in the blood, as is usually the case. The narcotic effect of CO_2, on the contrary, can be exerted upon any living cell, and it follows that an increase in the CO_2 tension of the blood can further depress the cells of the center when they have lost their specialized property of being stimulated by it. This is probably the explanation for depression of breathing, with little or no stimulation, after an animal whose breathing has been depressed by narcotics has taken a few breaths of air containing CO_2 (Fig. 266).

Another way in which CO_2 can cause respiratory depression in animals poisoned by narcotics is by stimulating the center when its oxygen supply is subnormal because of anoxemia, low blood pressure, or high cerebrospinal pressure (Fig. 262). This type of result, as we have already seen (page 666), may be obtained by any agent which increases the activity of the center (and therefore its need for oxygen) when its oxygen supply was barely sufficient for its needs before it was stimulated. The depression produced in this way is serious because it is due to a derangement of the vegetative functions of the cells and this is less readily reversible than a narcotic depression.

Still another way in which CO_2 in oxygen can cause cessation of breathing is by removing anoxemia (by virtue of the oxygen of the mixture) when afferent impulses aroused by anoxemia were the principal factor by which breathing was being maintained, as may be the case in profound narcotic depression (Fig. 265). If the gas mixture is supplied through a tracheal catheter, breathing may remain absent as long as the current continues to flow, but if it is inhaled in the usual manner, anoxemia soon reappears and breathing is resumed, though at a much slower rate than before (Fig. 265). An effect of this sort is not serious, and CO_2 cannot be said to be depressant in such a case; it is, however, without evident stimulant properties.

These observations indicate that the proper place of CO_2 in the treatment of severe respiratory depression is not to stimulate the center directly (in which it may be entirely unsuccessful, or if successful, dangerous), but to prevent reduction in the chemical stimulus of the blood by measures intended to combat anoxemia. The addition of 5 to 10 per cent CO_2 to the oxygen used for intratracheal insufflation, or inhalation of the mixture while artificial respiration is being employed, will prevent reduction in the CO_2 tension of the blood below the level at which the cells of the center are active and thus will assist in restoration of breathing when the deleterious influences of oxygen-lack and depressant agent are rectified by the procedures mentioned on page 668. In poisoning by carbon monoxide the addition of CO_2 to the inhaled oxygen has a special importance because it helps to release CO from its combination with hemoglobin. In all cases of severe respiratory depression, however, the all-important procedure is the administration of adequate amounts of oxygen; the addition of CO_2 is helpful in the sense noted above, but CO_2 should not be regarded as the life-saving agent.

ASPHYXIA NEONATORUM

Newborn infants who refuse to breathe spontaneously have always furnished a problem for the physician, but there seems little doubt that the condition is now being encountered more frequently than ever before. For this the use of nonvolatile narcotic drugs in dosage

large enough to produce unconsciousness, or at least amnesia, in the mother is undoubtedly responsible. The respiratory functions of the fetus have been studied intensively in recent years, and it is now possible to come closer to an understanding of fetal asphyxia than had previously been the case. The reader who is especially interested in this subject is referred to recent publications by Barcroft[117] and Windle.[165, 166] Until very recently it seemed probable that the fetus in utero normally makes respiratory movements by which amniotic fluid is drawn into the unexpanded fetal lungs, but the burden of evidence now is against this belief; respiratory movements in utero and aspiration of amniotic contents can occur, but only if the fetus is asphyxiated. Respiration of the fetus apparently can be stimulated either by increase in CO_2 tension or decrease in oxygen tension in the placental circulation, but the sensitivity to both stimuli is at best much less than in the adult and it is greatly reduced by narcotic drugs.

When these findings are considered in relation to existing information concerning the peculiarities of the circulation and the respiratory gas exchange in the fetus (Barcroft[116]) it becomes highly probable that asphyxia neonatorum is simply an extreme instance of respiratory failure due to oxygen-lack in the center. It is known that the arterial blood pressure of the fetus is low (less than 80 mm. in the sheep at term, and this animal is born in a much more developed state than man[115]); it is also known that the blood in the umbilical vein (which is the arterial blood of the fetal gas exchange) is only about 60 per cent saturated with oxygen while the normal human fetus is still *in utero*[51a]; when we remember that the arterial and venous circulations communicate by several channels in the fetus, it is evident that the blood which supplies the brain must contain considerably less oxygen than this, and it is probable that the actual figure is approximately half the 60 per cent saturation found in the umbilical vein. For these reasons alone we may conclude that the brain of the normal fetus must have been exposed to anoxia of high degree for some time before birth. In the process of birth the fetal anoxia is aggravated by the uterine contractions, which interfere with the gas exchange in the placenta; any direct interference with the circulation in the umbilical cord by pressing, pulling, or kinking would, of course, be an additional factor working in the same direction.

Table XXIII shows the average figures for the pH and oxygen and CO_2 content of blood collected from the umbilical veins of newborn human infants (Eastman[51c]). There are three groups of observations: the first comprises 7 infants delivered rapidly and spontaneously without anesthesia of the mother and one delivered by cesarean section under local anesthesia, this group representing the situation in an uncomplicated normal delivery without fetal asphyxia; the second group consists of 4 babies delivered by forceps with the mother under anesthesia by gas-oxygen-ether, representing moderate but not severe fetal asphyxia (all the babies of this group were crying actively within a minute after birth); the third shows the average of the results in 6 infants born in a state of severe asphyxia, to which three of them succumbed.

TABLE XXIII

AVERAGE GAS CONTENT AND PH OF BLOOD FROM THE UMBILICAL VEINS OF HUMAN FETUSES AT BIRTH (AFTER EASTMAN[51c])

	PH	CO_2 CONTENT (VOLS. PER CENT)	CO_2 TENSION (MM. HG)	O_2 CONTENT (VOLS. PER CENT)	O_2* SATURATION PER CENT
Normal delivery	7.36	45.9	35.5	10.6	51
Forceps delivery (recovery in all)	7.20	40.1	44.8	7.3	35.1
Severe asphyxia (fatal in 3 of 6)	7.04	37.5	61.6	1.3	6.3

*Calculated from an average oxygen capacity of 20.8 vols. per cent in fetal blood as given by Eastman.[51a]

From these results it is quite evident that the newborn child suffering from asphyxia has no deficiency of chemical stimulus to instigate respiratory activity, for the most nearly arterial blood in its body has a markedly reduced pH and a CO_2 tension nearly double that of the child in which breathing begins spontaneously; the lower CO_2 content is attributable to accumulation of lactic acid which Eastman[51b] has shown to occur in the asphyxiated infant—an uncompensated alkali deficit (page 646). The asphyxiated infant is suffering

from oxygen-lack of a degree seldom encountered in human beings, and the reason it does not breathe is that its respiratory neurons are so badly deranged by anoxia as to be unable to discharge impulses even though the stimuli to which they are subjected would ordinarily arouse them to maximal activity. Its inordinate sensitivity to depressant drugs is probably due to anoxia. Normally anoxemia stimulates breathing reflexly, but Snyder and Rosenfeld[151] believe that the carotid body mechanism has not yet begun to function at birth; this is in accord with the work of Clark[28] who found that the pressure reflexes from the aorta and carotid sinuses first appear four to six days after birth in dogs. The studies of Wilson and his collaborators[164] indicate that this is not true of the chemoreceptors of man, for they found the respiration of newborn infants to be strongly stimulated by lobeline—a drug which, as far as is now known, owes all of its stimulant effects on respiration to reflexes aroused by it in the carotid and aortic bodies. There is another and (to the writer) more attractive explanation for the failure of anoxemia to stimulate respiration in the fetus. We must remember that the fetus has been exposed to anoxia for a considerable time before birth, and though the consequences are not as drastic as they will be in the mature organism, this is only because the oxygen requirements of the fetus are lower than they ever can be when independent existence begins; furthermore, fetal anoxia is greatly exaggerated during birth; finally, the fetus has no stores of oxygen in the lungs to be drawn upon when the supply of oxygen from the maternal circulation is impeded during labor. If we correlate these with the additional fact that acute anoxia is undoubtedly able to depress neurons in general, including those of the respiratory center, we may conclude that the failure of acute anoxemia or asphyxia to stimulate respiration in the asphyxiated fetus is due to anoxic derangement of the neurons and not to absence of excitatory impulses from the chemoreceptors; further anoxia simply makes the neurons incapable of responding to any stimuli. The point has importance in connection with the treatment of this condition.

The *treatment* of asphyxia neonatorum, in the light of these studies, is clearly to be aimed at combating anoxemia, as Eastman pointed out some years ago. The administration of oxygen (preferably by tracheal catheter, with a pressure not higher than 12 mm. Hg[164]) is the first consideration; addition of 5 per cent CO_2 is desirable, not in the hope of stimulating the center (which CO_2 cannot do until the anoxic derangement is removed) but to obviate reduction in the CO_2 tension of the blood below the level at which the respiratory neurons are active. According to Wilson et al.,[164] lobeline injected into the umbilical vein before the cord is cut will immediately start respiration in a large proportion of these infants and thus lead to the greatly desired expansion of the chest and inflation of the lungs.* It is advisable to care for the oxygen supply before lobeline is injected because the anoxic depression will thus be most effectively counteracted and the risk of adding to it (by increasing the activity of the neurons when they are already suffering from severe anoxia) will be obviated. The use of analeptic drugs seems inadvisable; it is most unlikely that they could be any more effective in asphyxiated infants than they are in adults and they have been found occasionally to cause severe or fatal convulsions when given to infants even in the recommended dosage. Depression of the infant's respiratory center by narcotics given to the mother is probably a large item in severe fatal asphyxia (Cole[38] et al.). This effect is easier to prevent than to remedy; volatile narcotics, which are readily controlled and rapidly eliminated, are preferable to nonvolatile substances, and among the latter those which act for a short time are less objectionable than those with prolonged effects. The dosage should be kept as small as possible and the duration of the narcosis as brief as possible.

*According to Wilson[164] et al. the lungs of a stillborn baby cannot safely be inflated by positive pressure applied to the mouth or within the trachea, or by suction applied to the chest wall (Drinker respirator, page 705). Rupture of alveolar septa, hemorrhage, and subpleural emphysema will be produced without expansion of large areas of the lung. Perhaps this means that relaxation of the bronchial muscle, associated with a discharge of impulses from the respiratory center, plays a necessary part in the first inflation of the lung. If this is true, artificial inflation should be more effective when the bronchial muscle has been relaxed, as by adrenalin, but there is at present no information on this point. Wilson also points out that a gas exchange adequate for the basal needs of the infant whose lungs are unexpanded can be secured by intratracheal insufflation of oxygen (80 per cent) and carbon dioxide (20 per cent); it seems inadvisable to use as high a concentration as this of the latter gas, for the optimum stimulant concentration lies much lower and the concentration used to elicit narcosis in normal (not asphyxiated) subjects is not much higher.

CHAPTER XLV

ANOXIA

Anoxia means lack of oxygen, no matter where it is or how it is produced. *Anoxemia* means lack of oxygen in the circulating blood only; the two terms are not synonymous. *Hypoxemia* has recently been used to denote a reduction in the oxygen content of the blood short of the complete absence of oxygen that anoxemia implies if that term is taken literally; actually "anoxemia" has been used very widely for exactly the same purpose without any confusion, and the new word seems unnecessary. *Hypercapnia* means an increase and *hypocapnia* (or *acapnia*) a decrease in the amount of carbon dioxide in the blood; these terms imply that the oxygen content is not directly affected. *Hypercarbia* and *hypocarbia* have to do with changes in the alkali reserve. *Asphyxia* implies diminution both in the intake of oxygen and in the elimination of carbon dioxide, i.e., anoxemia plus hypercapnia; it is not a synonym for anoxia, although anoxia is one of the outstanding features of asphyxia.

THE CAUSES OF ANOXIA

Oxygen-lack may result from any one of a number of conditions. On the basis of their essential causes the anoxias have been classified by Peters and Van Slyke[126] as follows:

1. *Anoxic anoxia (anoxemia)* is reduction in the tension of oxygen in the arterial blood. It affects the entire body. It is produced by interference with the passage of oxygen from the air into the blood in the lungs (mechanical obstruction, drowning, weak respiratory movements, reduction in the size or permeability of the aerating surface by edema, exudate, consolidation, adhesions, collapse, or emphysema); by reduction in the partial pressure of oxygen in the inspired air (inhalation of inert gases such as nitrogen, hydrogen, nitrous oxide, ethylene, acetylene, helium, methane); and conspicuously by inhalation of air under reduced (barometric) pressure, as at the high altitudes reached on mountains or in flights in aircraft. Anoxemia may also be brought about by increasing the oxygen consumption until it is greater than the available supply; this can occur in very vigorous exercise even in normal subjects at sea level, but it is much more readily brought about at high altitudes or in subjects with a pre-existing defect in the pulmonary gas exchange.

2. *Anemic anoxia* is reduction in the volume of oxygen that can be furnished to the tissues by the blood. This results when the amount of hemoglobin is decreased (anemia, hemorrhage) or when the ability of the hemoglobin to yield oxygen to the tissues is decreased by poisons (carbon monoxide; agents, such as nitrites, nitrophenols, chlorates, and sulfonamide derivatives which change hemoglobin into methemoglobin). Here also the entire body is affected.

3. *Stagnant anoxia* is due to interference with the circulation. The amount of oxygen available in the blood may be normal, but if the circulation in the capillaries is impeded, the amount of oxygen reaching the tissues in a given time is less than they require. This type of anoxia may be *general* if the entire capillary circulation is sluggish (shock, hemorrhage, cardiac weakness, or low

arterial pressure for any cause, or abnormally high venous pressure, as from cardiac decompensation or venous obstruction). It may be *local* if the circulatory disturbance is local (spasm of arteries, as in Raynaud's disease, occlusion of arteries by embolism, or reduction of their size by diseases or poisons which cause gangrene). We have already (Chapter XLIV) encountered a special instance of this type in the cerebral circulation, where spasm of vessels may result from reduction in the CO_2 tension of the blood and where the capillary circulation may be impeded by rise in intracranial pressure.

4. *Histotoxic anoxia* is produced by interference with the ability of the cells to utilize oxygen, even though the supply is normal in all respects. This occurs most conspicuously in poisoning by cyanide, to a lesser extent in poisoning by alcohol and certain other narcotics.

THE EFFECTS OF ANOXIA

The central nervous system and the heart are the parts of the body from which arise most of the symptoms and practically all of the dangers of anoxia. Of all the tissues of the body these are the most sensitive to reduction in their own oxygen supply. The voluntary muscles are also affected directly, but the most serious effects of anoxia upon the muscular system are due to derangements in the central nervous system leading to faulty coordination and lack of voluntary control. Functions such as respiration, circulation, digestion, and metabolism, are altered by anoxia but the alterations are brought about by the regulating mechanisms of the central nervous system. Death from acute anoxia is due to damage to the heart and to the central nervous system. When the exposure is long-continued but less severe other tissues are likely to be involved, but changes in the central nervous system and cardiac weakness are still the most prominent features.

Fulminating Anoxia.—If anoxia of high degree is induced very rapidly (as by inhalation of an undiluted inert gas such as nitrogen, hydrogen, nitrous oxide, ethylene, helium, or methane), there will be an initial sensation of suffocation followed very rapidly by unconsciousness; in normal individuals the time required ranges from forty-five to eighty seconds. If the exposure is brief, recovery is just as rapid and quite complete when pure air is again breathed.* Such results are obtained only when the oxygen tension in the alveolar air is almost explosively reduced to a very low level, and this cannot be tolerated for more than a few minutes without danger of acute failure of the heart or of slowly reversible or irreversible damage to the central nervous system (see page 683). In such cases breathing is greatly stimulated at first and blood pressure and pulse rate are apt to increase sharply (Fig. 267), but if more oxygen is not soon supplied respiration becomes slower, and then fails entirely; blood pressure also soon begins to fall, the heart becomes slower, and soon it ceases to beat (Fig. 268). This type of fulminating anoxia is encountered daily in the use of nitrous oxide, undiluted with oxygen, in the practice of dentistry. It is also met with occasionally in mining accidents involving methane gas. A similar situation may also arise if there is a sudden failure in the source of oxygen in an airplane traveling at a high altitude; it is particularly to be

*As an example of the rapidity with which the effects of such an exposure develop and disappear, Haldane[58] cites the case of a miner who, upon raising his head into a pocket of methane, drops as though felled, recovers completely after breathing pure air for a few seconds, imagines that one of his companions had knocked him down, and acts accordingly.

expected in a sealed-cabin plane in which the occupants are breathing outside air that is mechanically compressed to a pressure approaching that found at sea level, for here a sudden leak in the cabin or failure in the compressing mechanism could cause a very rapid drop in the tension of oxygen in the inspired air (see Armstrong,[8] pp. 264, 335, and 387). Inhalation of hydrocyanic acid fumes also produces almost instantaneous unconsciousness and collapse, but the anoxia here is histotoxic, not anoxic. Inhalation of a high concentration of carbon monoxide gas will also produce almost immediate unconsciousness and collapse, but monoxide is not an inert gas since it combines chemically with hemoglobin (which the inert gases do not); recovery after an exposure to an atmosphere of CO would certainly not be as rapid as after inhalation of the other gases mentioned above.

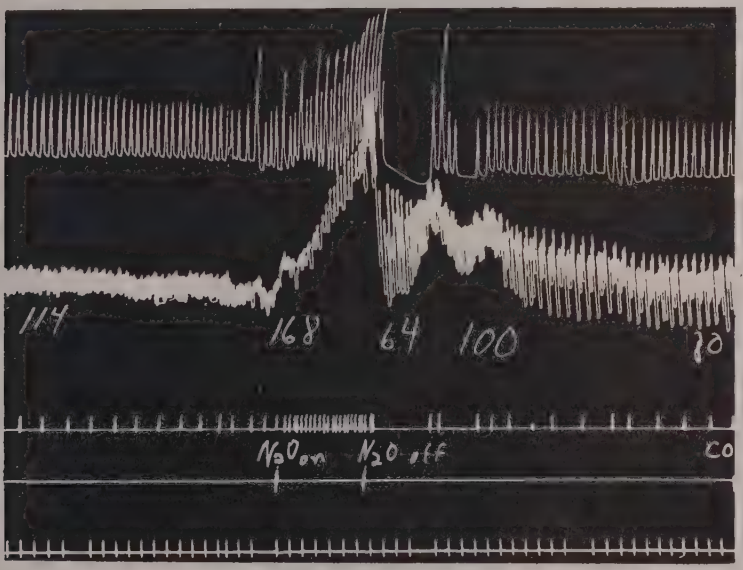


Fig. 267.—Fulminating anoxia. Dog—anesthesia by chloralose and morphine. Records (from above down): Respiration, femoral blood pressure, volume of expired air (in 500 ml.), signal, time in five-second intervals. Sinus and vagodepressor nerves intact. Between signals nitrous oxide (undiluted) was inhaled through the inspiratory valve. Note hyperpnea, hypertension, and cardiac acceleration (figures for pulse rate are directly under the blood pressure record). Note also apnea and fall in blood pressure immediately after removal of N_2O (i.e., after one breath of air).

Acute Anoxia.—As a rule, a deficiency of oxygen of a degree sufficient to produce definite symptoms does not appear instantaneously but develops more gradually. We shall deal later with anoxia due to disease and confine our attention at present to anoxia produced in normal individuals by changes in the environment. An outstanding example is exposure to an atmosphere containing a reduced amount of oxygen per volume of air breathed, as at the high altitudes encountered by aviators, mountain climbers, and travelers in mountainous country; similar situations may be created intentionally in the laboratory by exposing the subject in a closed chamber to an atmosphere under the reduced pressure cor-

responding to a high altitude, or by causing him to breathe air containing an abnormally high proportion of nitrogen, or by allowing him to breathe the same air in and out of a container with provision for absorbing the expired CO_2, so that he is exposed to a steadily decreasing oxygen tension as a result of his own consumption of the gas. In all such cases there are fewer oxygen molecules per ml. of inspired air and those present diffuse less readily. Another outstanding example—and one of great importance because it is likely to be encountered by any physician—is exposure to carbon monoxide. The effects of acute anoxia

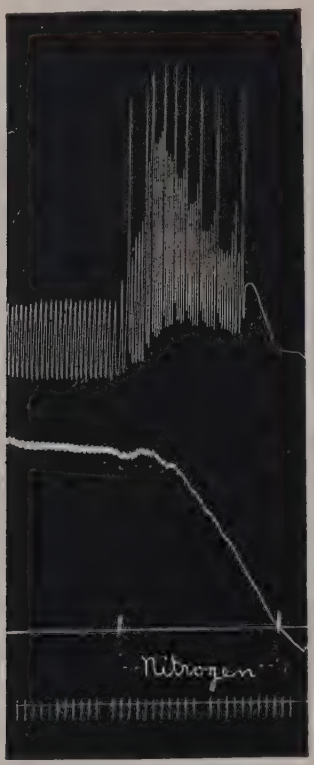


Fig. 268.—Effect of fulminating anoxemia on respiration and blood pressure. Cat—pentobarbital narcosis. Respiration recorded by plethysmograph, blood pressure by mercury manometer connected with femoral artery. Vagodepressor and sinus nerves intact. Inhalation of nitrogen (undiluted) until respiration failed. Note dyspnea followed by respiratory failure while blood pressure was falling rapidly because of cardiac depression. Time record shows five-second intervals.

produced in otherwise healthy subjects by any of these means are substantially the same. Different individuals vary considerably in their capacity to resist anoxia, and there are certain variations dependent upon the circumstances of the exposure (muscular exercise, rapidity of development of the anoxia, duration of the exposure, previous exposures not fully recovered from). On the whole, however, the symptoms which result from anoxia of a given degree of

severity are quite similar no matter how the condition is produced.* The chief symptoms arise from the central nervous system, the circulation, and the voluntary muscles.

The Central Nervous System.—The effects of acute anoxia bear striking similarities to those of acute alcoholism;[12, 13, 67, 113] this is best seen when muscular exertion and consequent fatigue are not a factor, and since the best example of this—ascent in aircraft—is also one of the most important practically (other examples are travelers ascending a mountain by a railroad, victims of poisoning by carbon monoxide, and subjects of a laboratory experiment), we shall now deal entirely with the symptoms and physical signs that are likely to be encountered during flight from sea level to a high altitude. Krogh[95] points out that animal flight (by birds) involves stresses greater than any other form of muscular activity; flight by man (in aircraft) also involves stresses that are new to the mammalian organism and against which it is without adequate protection. Perhaps the chief hazard is the absence of physical or mental discomfort, pain, or distress, to give warning of the presence of anoxia of a dangerous grade. This is because the cortical cells involved in the perception of sensations of pain or discomfort are among the first to be inactivated by progressive anoxemia (see page 683), so that the usual warning signals pass unheeded at the time; they are perceived only after the anoxemia has been relieved, presumably because the cortical cells recover more rapidly than the structures from which the sensations of pain and discomfort arise. Table XXIV, reproduced from Armstrong's book, will aid the reader in understanding the relation of altitude to anoxia.

TABLE XXIV

BAROMETRIC PRESSURE AT VARIOUS ALTITUDES*

ALTITUDE FEET	PRESSURE MM. HG	ALTITUDE FEET	PRESSURE MM. HG	ALTITUDE FEET	PRESSURE MM. HG	ALTITUDE FEET	PRESSURE MM. HG
0	760.0	21,000	334.8	41,000	134.2	61,000	51.6
1,000	733.0	22,000	320.8	42,000	127.9	62,000	49.2
2,000	706.6	23,000	307.4	43,000	122.0	63,000	46.9
3,000	681.0	24,000	294.4	44,000	116.3	64,000	44.7
4,000	656.4	25,000	282.0	45,000	110.9	65,000	42.6
5,000	632.4	26,000	269.8	46,000	105.7	66,000	40.7
6,000	609.0	27,000	258.2	47,000	100.8	67,000	39.8
7,000	586.4	28,000	246.8	48,000	96.0	68,000	37.0
8,000	564.4	29,000	236.0	49,000	91.6	69,000	35.2
9,000	543.2	30,000	225.6	50,000	87.3	70,000	33.6
10,000	522.6	31,000	215.4	51,000	83.2	71,000	32.0
11,000	502.6	32,000	205.8	52,000	79.3	72,000	30.5
12,000	483.2	33,000	196.4	53,000	75.6	73,000	29.1
13,000	464.6	34,000	187.4	54,000	72.1	74,000	27.7
14,000	446.4	35,000	178.7	55,000	68.8	75,000	26.5
15,000	428.8	36,000	170.4	56,000	65.5	76,000	25.2
16,000	411.8	37,000	162.4	57,000	62.5	77,000	24.0
17,000	395.4	38,000	154.9	58,000	59.6	78,000	22.9
18,000	379.4	39,000	147.6	59,000	56.8	79,000	21.9
19,000	364.0	40,000	140.7	60,000	54.1	80,000	20.8
20,000	349.2						

*From Armstrong: Principles and Practice of Aviation Medicine, Baltimore, 1939, Williams and Wilkins.

At altitudes lower than 12,000 feet (483 mm. barometric pressure or about 100 mm. oxygen pressure, corresponding with inhalation of about 13 per cent oxygen at sea level) most subjects have no symptoms and show no signs other than a moderate increase in respiratory activity of which they usually are unaware. At or above this altitude some or all of the following symptoms are likely to develop: sleepiness, headache, lassitude and fatigue, or a sense of comfort and well-being, a feeling of self-satisfaction associated with outbursts of hilarity or quarrelsomeness, and, in any case, breathlessness; frequently a vague, elusive feeling of distress or anxiety appears, indicating that the signals of danger are indeed present though imperfectly apprehended. Signs of muscular incoordination begin to make

*In carbon monoxide poisoning respiration is not stimulated as it is in anoxia of comparable severity produced by most other means (see page 692).

their appearance, and although simple, familiar movements may be performed about as well as usual, more complicated or unusual ones are clumsily and imperfectly executed. As the exposure continues muscular movements in general become slower and weaker, tremors appear, and finally paralysis develops. This begins in the legs and ascends until the arms and neck are also involved. At the same time memory is blunted and the sense of judgment and the capacity for self-criticism are impaired, so that the victim is unaware of his shortcomings and inefficiency; on the contrary, he is apt to be convinced that he is staging a remarkably good performance, and afterward he has no recollection of any difficulties encountered. Visual acuity begins to be impaired at about 15,000 feet, hearing at about 16,000-18,000. Pain perception and the appreciation of time are interfered with quite early. Above 20,000 feet muscular twitchings or clonic movements may appear and a striking fixity of purpose becomes evident: the subject now is incapable of reasoned judgment but instead persists with great tenacity in doing whatever task he is engaged in regardless of the consequences. Unconsciousness usually ensues at about 25,000 feet (oxygen pressure about 59 mm., corresponding with inhalation of about 8 per cent oxygen at sea level); by this time the victim may be unable to move and almost blind and deaf, yet he may not have been aware at any time of any abnormality. Death apparently is due to paralysis of the respiratory center in subjects with normal hearts, but the anoxia of high altitudes will greatly exaggerate any preexisting cardiac weakness, and cardiac failure may occur at relatively low altitudes in such individuals.

The circulation shows an increase in pulse rate beginning at about the same level as that at which the respiratory response begins (i.e., anywhere between 4,000 and 12,000 feet) and progressing up to the point of collapse. The average increase in normal subjects is about 28 beats per minute, but it may be considerably greater than this. The *blood pressure* also should begin to increase at the same time as the pulse rate and the increase in systolic pressure is progressive until collapse occurs. The rise in pressure should amount to 15 to 20 mm. but in some subjects the pressure falls quite early (apparently because of failure of the vasomotor center) and in these fainting is apt to occur. Cyanosis usually is present, but in subjects who faint pallor is seen instead. The *blood* shows no significant increase in hemoglobin or number of erythrocytes during short (four hour) exposure to 12,000 feet (Armstrong,[8] p. 269); the characteristic adaptation to high altitudes (page 691) apparently requires continuous exposure for a fairly long time. The *heart muscle* is depressed by anoxia; although Armstrong[8] (p. 268) has found that the hearts of experimental animals continue to beat for five or ten minutes after respiration has failed at high altitudes, the blood pressure (hence the amount of work done by the heart) apparently is very low under such circumstances, and it is most probable that the heart will fail very rapidly when exposed to severe anoxemia if the demands made upon it are of a normal order; from this viewpoint fainting at a high altitude is a protective reaction which safeguards the heart by lowering the blood pressure and thus diminishing the work demanded of the cardiac muscle. There is no doubt that exposure to the anoxemia of high altitudes is especially dangerous for subjects with impaired heart function.

The accompanying chart (Fig. 269) taken from the "Air Service Manual" of the United States Army depicts the results obtained in a normal individual when the oxygen content of the inspired air is gradually lowered by rebreathing while the exhaled carbon dioxide is absorbed. This particular subject withstood oxygen deficiency without alarming symptoms until a percentage of a little more than 6 was reached—a figure that corresponds with a barometric pressure of 217 mm., an altitude of about 31,000 feet, and an oxygen tension of about 44 mm. in the inspired air (159 mm. at sea level). Respiratory minute volume did not change significantly until the oxygen content of the inspired air had fallen nearly to 12 per cent, which corresponds with a barometric pressure of 434 mm., an altitude of about 14,500 feet, and an oxygen tension of about 91 mm. in the inspired air. As we have already seen (page 565), Ellis[52] has found that some subjects show a perceptible increase in respiratory minute volume when the oxygen content of the inspired air is reduced only to 18 per cent (corresponding with an altitude of about 4,000 feet). A significant hyperpnea usually begins only at about 14 per cent oxygen (12,000 feet, 483 mm. barometric pressure, 123 mm. oxygen tension in the inspired air), and the respiratory minute volume is doubled in most men by the time 8 per cent oxygen is reached (about 24,500 feet, 289 mm. barometric pressure, 60 mm. oxygen tension).

In mountain climbers breathlessness and fatigue are the most prominent symptoms, but this is because such subjects are exerting themselves more than the aviator. The greater

breathlessness is due to the greater carbon dioxide production consequent on muscular activity; the chemical stimulus to the respiratory neurons is not reduced to as low a level by the reflex hyperpnea of anoxemia as it is in subjects who are not exerting themselves and the center is therefore more strongly stimulated at a given grade of anoxemia. Another factor operating in the same direction is the relatively high CO_2 tension in the blood associated with muscular exercise at high altitudes; the alkali of the blood, which is prominently concerned in the transport of CO_2 (Chapter XLIII), is diminished by anoxia, and as a result an unusually large proportion of the total amount of CO_2 must be carried in solution and the CO_2 tension of the blood is easily raised. This breathlessness protects the mountain climber from foolhardy exposure to anoxia of a dangerous degree because he becomes much

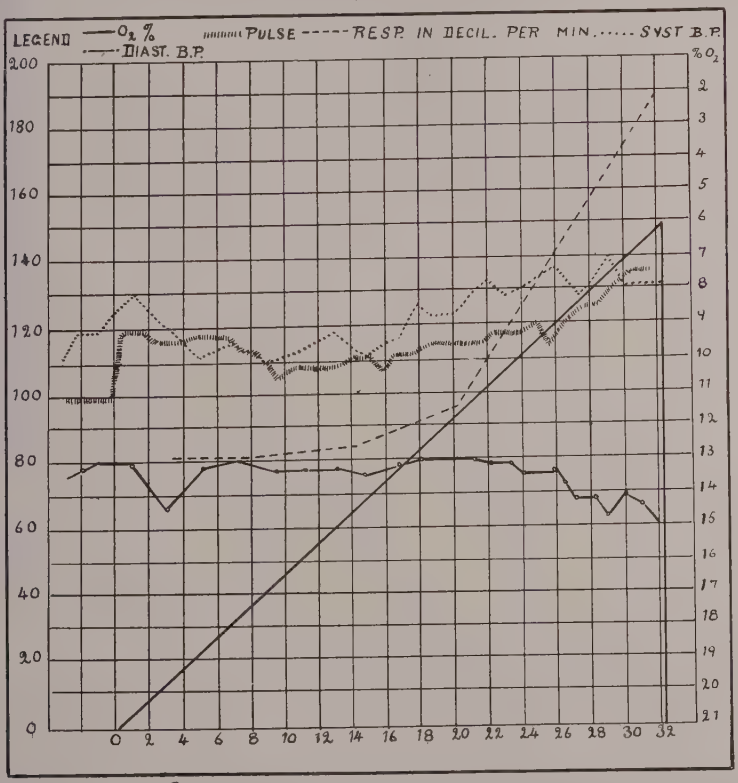


Fig. 269.—Response of a normal young man to progressive anoxemia. At start, records (from above down) show: Systolic blood pressure, pulse rate, respiratory minute volume (in 100 ml. units), diastolic blood pressure (key given at top of chart). Vertical ordinates: figures on left apply to blood pressure (mm. Hg), pulse rate, and respiratory minute volume; figures on right indicate percentage of oxygen in the inspired air, change of which is shown by continuous diagonal line. Abscissa: time in minutes. (U. S. Air Manual Chart.)

more uncomfortable than is the case with one who is borne upward without exertion on his part. The same increase in the CO_2 tension of the blood which causes breathlessness in mountain climbers may also safeguard their mental processes by keeping their cerebral blood vessels from constricting as they otherwise would when respiration is stimulated by anoxia (see page 610). The fatigue and muscular weakness of mountaineers are doubtless due in part to impairment of the oxidative processes in the muscles, in part to interference with the central nervous processes concerned with voluntary movement.

In the victim of *carbon monoxide poisoning* there is a greater tendency to fainting and unconsciousness and less respiratory distress than in anoxemias of comparable severity produced by other means (Haldane[67]). This is partly because monoxide has a dual effect on the hemoglobin of the blood: it diminishes the amount of oxygen that can be carried by the arterial blood and also makes the blood in the capillaries cling more tenaciously to whatever oxygen it contains (Peters and Van Slyke[126]). Consequently, the anoxia produced by monoxide is much more severe than would be expected from the degree of anoxemia (reduction in O_2 content of the blood) that is present, and the subject's heart and central nervous system are more dangerously poisoned than is at first apparent. Furthermore, in CO poisoning the oxygen tension of the arterial blood is normal though the amount of oxygen available to the tissues is reduced; consequently the receptors of the carotids and aorta are not stimulated although the tissues in general do not get enough oxygen.

The severity of the symptoms elicited by exposure to a deficient supply of oxygen is determined not only by the degree of the deficiency but also by the duration of the exposure. In the case of anoxia due to carbon monoxide these relationships have been worked out quite precisely (see page 693). Although the corresponding data for exposure to high altitudes have not as yet been obtained there is no doubt that the same general relationships exist here also. This same question, as it concerns the problem of flight in aircraft, is discussed by Armstrong.[7, 8] During the first World War it was found that aviators who made frequent flights at high altitudes without oxygen showed much greater fatigue and "staleness" than others who carried out similar assignments using oxygen. Some of the former developed a characteristic neurosis in which emotional instability, loss of self-reliance, suppressed anxiety, lack of initiative, muscular tremors, and disturbed sleep were outstanding symptoms.[113] As this syndrome developed the flier had to be kept at lower and lower altitudes and finally he became entirely unfit for flying although perfectly fit physically. Subsequent experience in civilian aviation has been very similar to this (see Armstrong,[8] pp. 279 ff.). There is no doubt that repeated exposures to reduced oxygen pressures can produce marked deterioration in cerebral functions. Evidently the brain does not recover completely from a brief exposure to severe anoxia, or from a prolonged exposure to moderate anoxia, until many hours (twenty-four to seventy-two hours—Armstrong[8]) have elapsed, and the more severe the anoxia or the longer the exposure, the longer the time required for complete recovery. If the exposure is repeated before recovery has taken place, it will have cumulative effects, i.e., the derangements produced by today's exposure are superimposed on the remains of yesterday's. The most vulnerable parts of the brain then show signs of damage between exposures. The situation here is undoubtedly very similar to that encountered after prolonged inhalation of nitrous oxide and oxygen; in some subjects this produces permanent degenerative lesions in various parts of the brain (Courville[92]). This shows that moderately severe anoxemia, continued over the relatively brief period of ordinary surgical anesthesia, is quite capable of producing irreversible changes in the central nervous system in some subjects, at least. We can safely conclude that there is a narrow and uncertain margin of safety between completely and promptly reversible neuronal derangements, on the one hand, slowly reversible or irreversible changes on the other.

Chronic Anoxia.—The effects of prolonged or repeated exposure to a subnormal supply of oxygen resemble fatigue just as closely as those of acute exposure resemble drunkenness (Barcroft[12, 13, 15]). The resemblance refers to mental as well as to muscular fatigue, and this fact is a matter of considerable interest to the physician.

The symptoms of acute anoxia do not disappear immediately when the normal oxygen supply is restored. If the exposure is short, the *aviator* as he returns from a flight at a high altitude, the *traveler* who has spent only a few hours on a mountain top and then returns to a lower altitude, or the *subject of a laboratory experiment* as the oxygen pressure is increased from a severely low level, notices first that lights are brighter and sounds are louder. Muscular power, judgment, and self-criticism return. By the time the surroundings have become normal there may only be a blank memory and a severe headache to remind the subject of his experience, although breathing and pulse are likely to be abnormally slow for some time. The longer the exposure lasts, the slower is the recovery when normal conditions are restored. Emotional disturbances, nausea, or weakness may continue after the subject has returned to

sea-level conditions, and may, in fact, appear only after the return to sea level if the sojourn at the higher altitude did not last long enough for these symptoms to develop there.

In the *dweller at high altitudes* compensatory factors come into play (see page 688), and the central nervous effects of acute anoxia become progressively less marked. Some of them remain in the form of decreased patience with one's self or with one's fellows, lessened ability to concentrate, decreased quality in the performance of tasks involving mental or physical work, and greater liability to fatigue, mental as well as muscular. Sleep is likely to be fitful, interrupted by dreams, and not refreshing. Pulse rate and blood pressure become normal again (Lutz and Schneider[107]) but breathing remains deeper and faster than at sea level. Muscular capacity improves, but it is less than normal, partly because shortness of breath promptly ensues, partly because the oxidations within the muscles are not as well carried out as they should be. Fatigue results from relatively slight exertion and recovery is unusually slow, with an undue amount of stiffness.

Natives who spend their entire lives at high altitudes become completely acclimatized, but occasionally they suffer from a set of symptoms which are known as *chronic mountain sickness*. The symptoms include headache, hoarseness, loss of appetite, weakness and pains in the extremities, visual disturbances, transient spells of stupor or coma. They occur without obvious cause in persons who have lived for many years without symptoms at the same altitude; they are likely to disappear spontaneously but to return with increasing severity. The cause is unknown: these patients show the same changes in the blood and in the chest as other natives symptom-free at the same altitude, and there is no evidence that any of the mechanisms of acclimatization are at fault. Talbot and Dill[156] in discussing the possible causes, point out that pathological changes may occur in the tissues after many years of exposure to subnormal oxygen tensions; they also suggest the possible influence of the abundance of ultraviolet rays at high altitudes. Apparently no one is immune to chronic mountain sickness, provided that he lives at a sufficiently high altitude for a sufficiently long time. There is experimental evidence to indicate that degenerative changes may occur in the organs of individuals who remain at high altitudes. Campbell[32] found that rabbits, rats, and mice kept under an atmosphere corresponding to that on Mt. Everest (30,000 feet—7 per cent oxygen) lost weight and eventually died; at autopsy fatty degeneration of the heart muscle and of other viscera was disclosed.

THE SIGNIFICANCE OF ANOXIA

The similarity between the symptoms of acute anoxia and those of acute alcoholism has already been alluded to. A feeling of comfort, well-being, and self-satisfaction, impairment of muscular coordination, distortion of judgment, emotional instability, blunting of sensory perceptions, loss of the power of self-criticism, loss of memory, and finally loss of consciousness—all these are common to both conditions and denote effects upon the central nervous system. Does this mean that alcohol and anoxia affect the central nervous system in the same way? The narcotic action of alcohol probably is due to an interference by it with the intracellular oxidative reactions upon which nerve cell function depends, and according to current conceptions[91, 133] this interference is exerted first and foremost on the dehydrogenating part of the cell enzyme system. Under such circumstances oxygen is taken up and activated in a normal manner, but it does not combine with hydrogen as it should (i.e., the oxygen carriers are normally oxidized but imperfectly reduced (see Chapter XLVII). Anoxia presumably acts by interfering with the uptake of oxygen by the cell simply because fewer molecules of oxygen are available for the process; the rate at which they diffuse into the cells may also be diminished. The end result, as far as the capacity of nerve cells to carry on their specialized functions is concerned, would be the same in anoxia as in narcosis, i.e., their ability to respond to stimuli would be decreased because the energy-yielding reactions which lead to the instability (excitability) on which the specialized functions depend are not properly carried out (see page 562). The similarity between the cerebral effects of alcohol and those of anoxemia indicates that the various brain cells have the same susceptibility to the two influences. The cerebral functions most recently acquired in man's evolutionary development (judgment, reason, self-criticism, self-control) are most susceptible to alcohol and to narcotics, while the more primitive functions concerned with muscular control are more resistant, and the most primitive ones (control of respiration, circulation, etc.) are most resistant of all. The reason for these differences in susceptibility is probably the same in both cases, i.e., differences in complexity of the various neuronal systems.

The highest cerebral functions presumably involve a larger number of neurons (which individually may also be more complex) and more synaptic communications, than the more primitive processes; since the entire organization is maintained in a reactive state by oxidative reactions within the individual neurons, a given degree of interference with these oxidations naturally manifests itself first and foremost in those parts in which the most cells are concerned in the normal response. Another probable factor in these differences in susceptibility is a difference in the strength of the excitation process; the disturbances which normally activate the higher cerebral functions probably are distinctly weaker than those involved in muscular movements and those concerned in the regulation of medullary functions are probably the strongest of all (page 663). If the excitability of the entire system is reduced to the same extent, either by alcohol or by anoxia, the weaker signals would naturally become ineffective before the stronger ones.

In *chronic anoxia* the resemblance to muscular fatigue has been stressed for a number of years (Barcroft), and there is ample reason in the known facts of muscular contraction to account for this resemblance. We are entitled to believe that the muscles actually become fatigued more readily because the blood contains a subnormal supply of oxygen. A similar relation between anoxia and fatigue of the central nervous system was also pointed out by Barcroft[14] and has aroused considerable interest on the part of neurologists and psychiatrists (see McFarland[113]). When we peruse the list of the symptoms of chronic anoxia, as encountered in aviators and in dwellers at high altitudes, we find a close resemblance to the symptoms of an impending nervous breakdown or with those of an established neurosis. Decreased patience, emotional instability, lessened ability to concentrate, constant fatigue, unrefreshing sleep, muscular twitchings, loss of self-confidence, anxiety—these are phenomena which the physician frequently encounters in patients who are not suffering from anoxia of any demonstrable cause. There is as yet no evidence to indicate that lack of sufficient oxygen, or a perversion in the normal oxidative processes of the cerebral cells, is responsible for the neuroses and psychoses which form a large and ever-growing problem of modern life, but the possibility is an attractive one. Abnormal contraction of the cerebral blood vessels has long been regarded as a probable factor in producing functional disorders of the brain, and this would mean stagnant anoxia. Loevenhart and his co-workers[101] found that inhalation of CO_2 produced temporary relief in some severe psychoses, and this has been repeatedly confirmed; the most probable explanation of the improvement is that it is due to relaxation of spasmodically contracted cerebral blood vessels. Yet we must not lose sight of the undoubted fact that the function of cerebral nerve cells can be altered by many agencies of which anoxia is only one; the end-result may be the same although the cause is entirely different. The fact that the symptoms of chronic anoxia are similar to those of certain functional disorders of the brain may only mean that the same nerve cells are deranged in both but for entirely different reasons.

It is a striking fact that the defenses of the body against anoxia are usually kept in reserve and are drawn upon only in emergencies. Under ordinary circumstances the call for oxygen is met by the respiratory stimulant action of CO_2 alone. As a rule, increased call for oxygen and increased production of CO_2 run hand in hand, and the stimulant action of CO_2 on the respiratory center brings about the increased pulmonary ventilation required to meet the call for oxygen. This is a fortunate provision because CO_2 is not as harmful to the cells as anoxia, because CO_2 works more rapidly by reason of the ease with which it penetrates cells, and because CO_2 has a specific action in regulating the tone of cerebral blood vessels. As long as respiration is regulated by CO_2 the central nervous system is in little danger.

The hyperpnea due directly to oxygen-lack is different in several important respects from that due to CO_2 excess. In the first place, the response to anoxemia is mainly due to reflexes from the chemoreceptors, while that to CO_2 is the result of the direct effect of CO_2 upon the respiratory center. A possible reason for this peculiar location of a defense against anoxia has been suggested on page 597. Also, the sensitivity of the reflex receptors to oxygen-lack is much less than the sensitivity of the center to CO_2. Ellis[52] found that it is necessary to reduce the oxygen in the inspired air to about 8 per cent (normal about 21 per cent) to double the volume of breathing, whereas Haldane and Priestley[68] found an increase of 0.22 per cent in the CO_2 content of the alveolar air sufficient to do the same thing. Further, CO_2 seems to be a specific dilator of cerebral blood vessels as well as a specific stimulant to breathing, so that as long as the CO_2 tension of the blood rises the entire central nervous system will get more blood; but once anoxemia begins to drive respiration, the CO_2 tension of the blood is reduced and the cerebral vessels are likely to constrict because the constrictor effect of lowered

CO_2 tension is stronger than the dilator influence of decreased oxygen tension. In this way a vicious circle is set up: anoxemia stimulates breathing reflexly, lowers the CO_2 tension of the blood, and causes constriction of the blood vessels supplying the brain, thus increasing the anoxia to which the nerve cells are subjected. Finally, in extreme anoxia, there is an acidosis as the result of incomplete oxidations in the tissues[93]; this is almost a terminal event—an expression of extreme derangement in the metabolic activity of the cells.

CYANOSIS

The term *cyanosis* simply designates a blue color imparted to the skin or mucous membranes (or any other vascular bed) by a change in the chemical composition of the blood. Cyanosis is always due to a change in the blood and the color disappears when the blood is expelled from the tissue under observation; this fact distinguishes it from the coloration due to deposition of material (e.g., silver) outside the blood vessels. The most frequent and most important cause of cyanosis is an unusually large concentration of reduced hemoglobin in the blood, and this occurs in anoxemia or in stagnant anoxia. In the anemic and histotoxic forms of anoxia and in poisoning by carbon monoxide cyanosis does not occur, for reasons to be explained later. Cyanosis is also produced by the formation of any dark hemoglobin derivative, such as sulfhemoglobin or methemoglobin.

The blue color in cyanosis is due to the absolute concentration of reduced or otherwise unoxygenated hemoglobin in the capillaries and not to the relative proportions of reduced and oxygenated hemoglobin. It has been found (Lundsgaard[104, 105]) that about 5 grams of reduced hemoglobin per 100 ml. of capillary blood, or an oxygen unsaturation of 6.70 ml. per 100 (since 1 Gm. of hemoglobin can combine with 1.34 ml. of oxygen) is about the threshold level at which cyanosis appears. Consequently, an anemic subject who has less than 5 Gm. of hemoglobin per 100 ml. of blood (= an oxygen capacity of about 7 ml. per 100 or less) cannot usually become cyanotic. The cyanotic color in the skin or other surface is mainly due to the color of the blood in the capillaries. Since the blood is continually giving up oxygen during its passage through the capillaries the average unsaturation of the blood in its transit through them may be taken as the mean between the arterial and venous unsaturations; thus if A is the oxygen unsaturation of arterial and V that of venous blood, $\frac{A+V}{2}$ gives the average unsaturation of capillary blood. Normally, arterial blood is about 95 per cent saturated with oxygen; with a capacity of 21 ml. of oxygen per 100 this means that A = about 1 ml. of oxygen unsaturation per 100 ml. under normal conditions. Venous blood normally contains about 15 ml. of oxygen per 100, so that it is roughly 70 per cent saturated and V = about 6 ml. of oxygen unsaturation per 100. $\frac{A+V}{2}$ therefore would normally be 3.5 ml. of oxygen unsaturation, or about 2.6 Gm. of reduced hemoglobin, in each 100 ml. of blood in the capillaries. This must be practically doubled for cyanosis to occur, and it is evident that such a result could be obtained: (1) by increasing A with the arteriovenous oxygen difference unchanged (as in anoxemia, where the amount of reduced hemoglobin in the arterial blood is greater than normal), or (2) by increasing V with the arterial blood normally oxygenated (as by an increase in the utilization of oxygen by the tissue under observation, or by a decrease in the blood flow through it), or (3) by increasing both A and V at the same time (as in

muscular exercise in the presence of anoxemia, or in heart disease, where the aeration of the blood in the lungs may be impeded by fluid in the air passages while the circulation in the tissues is also abnormally slow).

Factors Which Modify Cyanosis.—Lundsgaard and Van Slyke[105] have pointed out that although the oxygen unsaturation of the blood in the capillaries is undoubtedly the real cause of cyanosis, there are other factors which modify the intensity of the color and which may influence the threshold concentration of reduced hemoglobin required to produce cyanosis. The most important of these factors are: (1) the thickness of the avascular epidermis, which may conceal to varying degrees the color in the capillaries; (2) the amount of pigment in the skin, whether normal (sunburn, or the deep pigment of the black and yellow races) or pathological (jaundice, argyria, Addison's disease, etc.); (3) variations in the color of the blood plasma, due to differences in the amount of pigment or lipoid in it, possibly also to large increases in the leucocytes, as in leucemia; (4) variations in the amount of oxygenated hemoglobin in the blood; (5) variations in the number, width, and length of blood-filled capillaries in a given area, including short circuits between the arterial and venous channels (arteriovenous communications); (6) deviations of the average capillary blood from its normal mean position between arterial and venous. These factors cannot produce cyanosis, but they can alter the amount of oxygen unsaturation needed to produce it as well as the final color produced.

Causes of Cyanosis.—1. *Increase in the Amount of Reduced Hemoglobin in the Arterial Blood.*—Cyanosis due to incomplete oxygenation of the blood is the most severe type and usually the most important from the standpoint of diagnosis and treatment. It should be made clear that while the presence of cyanosis (if due to abnormally large amounts of reduced hemoglobin in the capillaries) means that anoxia is present, the absence of cyanosis does not necessarily mean that anoxia is absent. The color of the skin is more directly related to the oxygen unsaturation of the arterial than to that of the venous blood, whereas the oxygen uptake by the tissues is more closely related to the oxygen unsaturation of the venous blood. Cyanosis increases with the amount of hemoglobin present because at a given oxygen unsaturation there will be more reduced hemoglobin; there may be marked cyanosis in conditions of *polycythemia* with little or no anoxemia. *Anemia*, on the contrary, decreases the tendency to become cyanotic while increasing the likelihood of anoxia. Acclimatization (page 688) reduces the symptoms of anoxia but cyanosis remains unchanged. *It is only in conditions in which anoxia is due primarily to imperfect oxygenation of the blood, in which the hemoglobin content of the blood remains unaltered, and in which the onset and course are too rapid for acclimatization to occur, that a close parallelism exists between cyanosis and anoxia. Such conditions exist in pneumonia and probably in other acute anoxias arising from interference with the gas exchange in the lungs.*

a. *Conditions in which the primary fault lies in the aerating surfaces in the lungs.* A characteristic example is the state of affairs in *lobar pneumonia*. Cyanosis in this disease is not entirely due to the reduction in the aerating surface by the consolidation, for in the consolidated areas the circulation may be obstructed and the blood therefore must pass through well-ventilated alveoli. But in some of the consolidated areas the vessels remain patent, and the blood passing through these emerges as venous as it entered. Fluid may be present in the finer respiratory passages and this interferes with the passage of air into alveoli in which the circulation is normal. Respiration is typically rapid and shallow in this disease, partly because of pleurisy which leads to voluntary restriction of the respiratory movements, partly because of a direct effect of the toxins upon the center; the impaired respiration adds to the anoxemia. The arterial blood leaving the lungs is a mixture of that which has been oxygenated and that which has not, and in severe cases there may be marked cyanosis, with the arterial blood only 75 per cent saturated with oxygen; this means an arterial oxygen content equal

to that normally seen in venous blood (15 ml. per 100). *Cyanosis is often more marked in bronchopneumonia than in lobar pneumonia* because the disease process is widely scattered, there is considerable fluid in the air passages, and the circulation in the consolidated alveoli is not abolished.

In cases of *obstruction of the trachea or bronchi* cyanosis results for obvious reasons. In *asthma* cyanosis occurs because the movement of air in and out of the alveoli is hindered by contraction of the bronchial muscle. In *emphysema* cyanosis may be very marked, partly because the chest is permanently in the inspiratory position and cannot be expanded much further, partly because many of the septa between the alveoli are obliterated and the area available for the gas exchange (both vascular and epithelial) is reduced. In *acute pneumothorax* cyanosis often occurs because the movement of air in and out of the collapsed areas is impeded while the circulation continues in them; in chronic pneumothorax the vessels become obliterated and cyanosis may be absent.

b. *Conditions in which the primary fault is insufficient pressure of oxygen in the alveolar air.* Exposure to the low barometric pressures found at *high altitudes* produces cyanosis and this is likely to occur when the pressure is reduced to about two-thirds of its sea-level value, i.e., to 500 mm., corresponding to an altitude of about 11,000 feet. The cyanosis persists after acclimatization. A similar situation may be created by *shallow breathing* even at sea level, for the air in the alveoli is not properly renewed and its oxygen tension falls. Rapid shallow breathing may be encountered in *neurasthenia, after gassing,* or in certain forms of *encephalitis.* One of the dangers of these conditions is that the respiratory center does not get a period of complete rest and it may become fatigued. Deep breathing is beneficial in such cases.

c. *Conditions in which the primary fault is an abnormal mixture of arterial and venous blood.* The characteristic form is seen in *congenital heart disease,* in which there is intense cyanosis in about half the cases. The cyanosis is of course partly due to direct mixture of blood between the two auricles, but not entirely so because oxygen inhalation relieves it considerably; this indicates that the low arterial oxygen saturation which these patients show is due to a considerable extent to imperfect oxygenation of the fraction of the blood which flows through the lungs. The intense cyanosis is also due to some extent to the polycythemia which is usually present; a given unsaturation of arterial blood would mean an unusually large amount of reduced hemoglobin in the capillaries.

In collapse, consolidation, or obstruction of the air passages as long as the circulation continues in the alveoli which are imperfectly aerated (if at all) the blood emerging from the lungs is also a mixture of oxygenated and unoxygenated.

2. *Cyanosis Due to Abnormal Reduction of Oxyhemoglobin in the Systemic Capillaries.*—This may be due either to increased utilization of oxygen by a tissue or to decreased flow of blood through it; the latter is the usual cause of cyanosis of this type, for whenever the metabolic activity of a tissue is increased the circulation is increased in proportion to its increased need for oxygen. Thus in *severe muscular exercise* cyanosis may occur in the face but the active muscles show little or none. Here the cyanosis is probably due to vasoconstriction in areas which do not participate directly in the increased activity, so as to divert more blood to those that do. *Chilling* of a part of the body causes cyanosis because the blood vessels constrict; excessive cold may reduce the metabolism of the chilled part and it then loses its blue color and becomes pale. In *heart disease* the peripheral circulation becomes abnormally sluggish and this is a factor in the production of the cyanosis which develops.

To produce cyanosis solely as the result of increased utilization of oxygen by the tissues the blood must lose 6 ml. more of oxygen per 100 than it ordinarily does, which means the development of *more than double the normal arteriovenous oxygen difference of 5 ml. per 100;* the oxygen consumption would have to be more than doubled.

3. *Cyanosis Due Both to Decreased Oxygenation of Arterial Blood and to Increased Reduction of Oxyhemoglobin in the Tissues.*—This is seen in the ap-

pearance or exaggeration of cyanosis in individuals at *high altitudes when they indulge in physical exercise.* It is seen in patients with *heart disease,* for in them the oxygenation of the blood in the lungs is hampered by fluid in the air passages and the peripheral circulation is sluggish; there may be no cyanosis until the patient exerts himself or it may be present continually, depending on the severity of the condition. The *asthmatic* or *emphysematous* subject is in a similar situation.

4. *Cyanosis Due to Alterations in the Hemoglobin.—Methemoglobin* is produced by a number of drugs and poisons among which nitrites, acetanilid, aniline, nitrobenzene, the nitrophenols, sulfanilamide and its congeners, and chlorates are conspicuous. The iron is changed to the trivalent form and cannot combine reversibly with oxygen. Such hemoglobin is dark in color and cyanosis appears as a result. The oxygen tension of the blood, however, is normal and the subjects may have no respiratory symptoms of anoxia although they are deeply cyanosed. The color of the skin is due to the methemoglobin, not to reduced hemoglobin.

Sulfhemoglobin is rare in its appearance and the conditions responsible for its formation are not yet understood. It is not formed in poisoning by sulfides because they are rapidly transformed to sulfates in the body, but in cases of sulfhemoglobinemia there is a strong reducing agent of unknown composition in the blood, urine, and saliva, and the suggestion has been made that because of this agent the minute amounts of H_2S normally absorbed from the bowel can convert hemoglobin into sulfhemoglobin.

In poisoning by carbon monoxide there is no cyanosis because carboxyhemoglobin is red, not blue, and the blood passes through the capillaries with less than the normal amount of reduced hemoglobin in it. *In poisoning by cyanide or other agents which produce a histotoxic anoxia there is also no cyanosis* because the tissues take less oxygen out of the blood than normally, and there is therefore less reduced hemoglobin in the capillaries than would ordinarily be the case.

COMPENSATIONS FOR ANOXIA (ACCLIMATIZATION)

When a normal individual first moves to a high altitude, he suffers from the usual symptoms of acute anoxia: breathlessness, nausea, vomiting, headache, palpitation, muscular weakness and incoordination, interference with mental processes, dimness of vision, partial deafness. The relation of the symptoms to the ascent of mountains has long been recognized and the term *mountain sickness* is applied to them. After a time (usually several days) the symptoms diminish in severity and some of them may eventually disappear entirely. The individual is now able to carry on a much greater amount of physical and mental exertion than was possible at first. *Acclimatization* has taken place. The most important factors responsible for this remarkable ability of the normal body to secure the oxygen it requires are *an increase in the rate and depth of breathing and an increase in the ability of the blood to transport oxygen.* In addition, it is probable that the tissues become adapted in some unknown way to a lower pressure of oxygen than that to which they were accustomed.

The rate and depth of breathing increase, the change in rate being proportional to the altitude (Haldane,[67] Barcroft[12]). As a result of the increased depth of breathing the oxygen tension in the alveolar air approaches that of the inspired air more closely than is the case when breathing is shallower, and the

blood is therefore exposed to a higher tension of oxygen. Thus, at 10,000 feet the alveolar oxygen tension would be 59 mm. and at 15,000 feet 33.8 mm. if the oxygen tension of alveolar air remained as much below that of the inspired air as it does at sea level. Actual determinations show a tension of 65 mm. at 10,000 feet and 52 mm. at 15,000 feet, the added pressure of oxygen in the alveoli being due to increased movement of air in and out of them. The increase in breathing is due to reflexes from the carotid and aortic bodies and the CO_2 content of the blood is accordingly reduced. The CO_2 tension in the alveolar air falls correspondingly. To compensate for the alkalosis which results from the lowered CO_2 tension there is an increased excretion of alkali by the kidney and

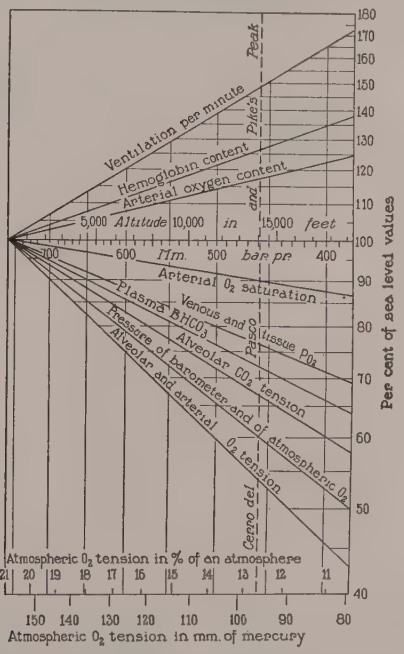

Peak
Ventilation per minute
Hemoglobin content
Arterial oxygen content
5,000 Altitude 10,000 in 15,000 feet
600 Mm. 500 bar pr. 400
Arterial O_2 saturation
Plasma $BHCO_3$
Venous and tissue PO_2
Alveolar CO_2 tension
Pressure of barometer and of atmospheric O_2
Alveolar and arterial O_2 tension
Cerro del
Atmospheric O_2 tension in % of an atmosphere
21 20 19 18 17 16 15 14 13 12 11
150 140 130 120 110 100 90 80
Atmospheric O_2 tension in mm. of mercury
Per cent of sea level values
180 170 160 150 140 130 120 110 100 90 80 70 60 50 40

Fig. 270.—Effects of residence at high altitudes sufficiently long for acclimatization. Results obtained by Barcroft's party in the Andes. (From Peters and Van Slyke: Quantitative Clinical Chemistry, Vol. I, Baltimore, 1931, Williams and Wilkins Co.)

the total amount of base in the blood is decreased. As a rule, this excretion of alkali does not quite compensate for the lowered CO_2 content and the hydrion concentration of the blood remains slightly more alkaline than at sea level (Barcroft,[15] Peters and Van Slyke[126]). We have already seen (page 680) that the reduction in the amount of alkali in the blood is partly responsible for the breathlessness which promptly occurs on exertion at high altitudes, even in acclimatized persons.

As a result of the greater alkalinity of the blood the affinity of hemoglobin for oxygen is increased (see page 633) and the blood can therefore carry a larger amount of oxygen to the tissues even without any increase in the amount of

hemoglobin present. But there is also an increase in the number of erythrocytes in circulation; this polycythemia is brought about first by contraction of the spleen,* subsequently it is added to and maintained by augmented activity of the bone marrow (Barcroft[15]).

Fig. 270 is a graphic presentation of the data obtained by the expedition led by Barcroft to the Andes in Peru. The altitude was 14,200 feet and the barometric pressure was 458 mm., which is about 60 per cent of the pressure at sea level (760 mm.).

The *circulation* of the acclimatized person is practically normal when no strain is put upon it, but its capacity for meeting a demand for increased blood flow is reduced. The members of Barcroft's party had the same pulse rates under basal conditions, i.e., when just awakened from sleep, when residing at high altitude and at sea level, but even the slight exertion of sitting was enough to maintain some acceleration of the heart at the higher altitude.[15] The amount of exercise required to produce a given acceleration of the pulse of an individual acclimatized to 14,200 feet was about two-thirds that required at sea level. From data supplied to him by the 1924 expedition to Mt. Everest, Barcroft concludes that the pulse may remain normal during rest up to an altitude of 16,500 feet, while above that level persistent acceleration occurs. The Everest party noted pulse rates of 160 to 180 per minute while climbing in the neighborhood of 27,000 to 28,000 feet. All the members who went above 27,000 feet had dilated hearts. These were carefully selected, healthy, trained subjects. There can be no doubt that life at high altitudes entails a strain on the heart even after acclimatization. Cardiac depression and failure are prominent among the dangers of life at high altitudes.

Acclimatization is not equally effective in all persons. Individuals whose breathing increases in depth are better off than those in whom the rate is affected predominantly. This fact is illustrated by the following figures:

	ML. PER RESPIRATION	NO. OF RESPIRATIONS PER MINUTE	HEIGHT IN METERS AT WHICH SYMPTOMS OCCURRED
Subject 1	270	20	3300
Subject 2	440	14	6000
Subject 3	700	8	6500

(After Halliburton)

In Barcroft's party those in whom oxygen passed through the alveolar membranes at the most rapid rate became most completely acclimatized, but the diffusion rate of oxygen did not increase at the high altitude in any of the subjects. The arterial blood was about 85 per cent saturated with oxygen in these men instead of the normal 95 per cent, and samples of blood drawn directly from an artery had a distinct bluish color. *There probably is no secretion of oxygen into the blood: the oxygen tension in the blood is never higher than that in the alveolar air.*

In persons who spend their entire lives at high altitudes the chest becomes permanently enlarged; these people look as though they had severe pulmonary emphysema, but their vital capacities are increased, not decreased as in emphysema. The decrease in vital capacity in emphysema is associated with oblitera-

*This is at least true of laboratory animals, such as the dog. It is doubtful whether the human spleen is capable of contracting to any effective extent, for smooth muscle is not found in its trabeculae or capsule.

tion of a considerable proportion of the pulmonary capillaries, but in the native dweller at high altitudes the size of the pulmonary capillary bed is not reduced; it may actually be increased by dilatation of these vessels (Talbot and Dill). These individuals are able to get more oxygen from the air into the blood than would otherwise be possible, first, because they can get a higher tension of oxygen in the alveoli at each breath, and second (if Talbot and Dill are correct), because the area over which the venous blood is exposed to the alveolar air is increased by dilatation of the alveolar capillaries. Their blood shows an increase in hemoglobin, in oxygen capacity, in number of erythrocytes, and in the proportion of cells to plasma (hematocrit). Table XXV gives pertinent data obtained by Talbot and Dill[156] in five natives who lived and worked at 17,500 feet in the Andes in Chile.

TABLE XXV

ARTERIAL BLOOD OF FIVE HEALTHY NATIVES AT 17,500 FEET

SUBJECT	O_2 CAPACITY ML. PER 100	O_2 SATURATION PER CENT	HEMATOCRIT PER CENT CELLS	ERYTHROCYTES MILLIONS PER C.MM.	WHITE BLOOD CELLS PER C.MM.
Ca	32.7	74.8	74.7	7.48	5,200
Al	29.2	78.3	62.2	6.85	7,400
Fr	24.6	84.6	52.2	6.15	8,300
Ba	30.7	70.2	73.0	7.09	6,500
He	34.2	67.6	81.8	9.10	5,000
Normal (sea level)	20.9	95	46	5.40	6,000

According to Hurtado[85] the erythrocytes of natives at an altitude of 14,890 feet are abnormally large, but each red cell contains less hemoglobin than at sea level; the surface over which the hemoglobin is exposed for the gas exchange in the lungs and tissues is therefore unusually great, and this may be one of the most important factors in complete acclimatization. He found, in increased resistance of such blood to hypotonic hemolysis and in the presence of young forms (including reticulocytes) among the cells, evidence of continued activity of the hematopoietic system. Talbot and Dill also found reticulocytes, in numbers ranging from 0.4 to 3.4 per cent, among the erythrocytes in the blood of their subjects at 17,500 feet.

For further details of this interesting subject the reader is referred to the monographs by Haldane,[67] Barcroft,[15] and McFarland.[113] The chemical changes in the blood are discussed by Peters and Van Slyke.[126]

ANOXIA IN DISEASE

Anoxia is known to occur in diseases which affect *respiration* (pneumonia, emphysema, atelectasis), *circulation* (cardiac decompensation, congenital malformations, shock), or *hemoglobin* (anemia, carbon monoxide poisoning, methemoglobinemia). Histotoxic anoxia may occur in disease (other than in poisoning by cyanide, alcohol, or other narcotics), but there is as yet no evidence that such is the case.

In considering the anoxia of high altitudes we have seen that among the dangerous features in that condition are a blunting of the victim's perception of the usual warning signals such as pain, discomfort, and distress, and a diminished appreciation of the course of events. In anoxia due to

disease exactly the same situation is encountered, but here the decrease in cerebral acuity may mercifully diminish the patient's suffering and thus assist the physician. It is highly important, however, that the physician be not deceived by the euphoria produced by cerebral anoxia and that he remember that the underlying process is a disorganization of cell function which may have disastrous consequences if it is not checked. When the physician finds that a very ill person feels much better, he must at once determine whether this means actual improvement in the disease process or the onset of cerebral anoxia, for the procedures indicated are of course entirely different in the two cases.

Pneumonia produces anoxemia, primarily by reducing the aerating surface in the lungs. In addition, breathing becomes rapid and shallow and this contributes to the anoxemia because it makes alveolar ventilation less efficient; rapid, shallow breathing also means less complete rest for the respiratory neurons which are already suffering from anoxia. Furthermore, the circulation in the consolidated areas of the lungs is practically abolished while that through the normal parts is accelerated, and the flow of blood may be so rapid in the undiseased alveoli that the absorption of oxygen is incomplete. The greatest danger of anoxemia in pneumonia is produced by obstruction of bronchi leading to unconsolidated areas (Stadie[152]), i.e., by *bronchopneumonia,* in which the circulation in the alveoli of the affected parts is not obstructed.

In chronic pulmonary disease, such as chronic bronchitis, asthma and emphysema, anoxia is present because the blood is insufficiently oxygenated in the lungs. Acclimatization occurs as in the dweller at high altitudes and there may be little or no discomfort as long as the subject is at rest. Like the mountaineer, however, his tolerance for exertion is greatly diminished and his heart is subjected to a constant strain which is dangerously augmented when, as in exercise, his other tissues need more oxygen.

In *cardiac decompensation* anoxia occurs for two reasons: (1) anoxemia results from the presence of fluid in the finer air passages, and from the emphysema which frequently accompanies it; (2) stagnant anoxia is produced by sluggishness of the circulation in the capillaries.

In *anemia* the circulation is probably accelerated so as to compensate in part for the diminution in the amount of oxygen carried by each unit volume of blood. A larger compensating factor appears to be adaptation of the tissues to a lower oxygen tension during the slow development of the disease (Peters and Van Slyke[126]). It is probable that dilatation of blood vessels is a prominent factor in this adaptation.

In *poisoning by carbon monoxide* we encounter a form of anoxia that is particularly dangerous because this toxic gas not only appropriates some of the hemoglobin and thus deprives the body of that much of its ability to transport oxygen, but also because the presence of monoxide combined with part of the hemoglobin makes hemoglobin molecules which are not actually combined with monoxide "cling to oxygen with abnormal tenacity."[126] Both CO and O_2 combine with the iron of hemoglobin, but CO has an affinity 210 times that of O_2 for human hemoglobin, and when both gases are present the relative amounts taken up by the blood follow that proportion.

Poisoning by carbon monoxide is a serious and common condition. The gas is formed by incomplete combustion of carbon; it may be evolved from a coal fire which has insufficient draft, or from a charcoal brazier. Considerable amounts of it may be present in mines as a result of explosions or of spontaneous oxidation of coal. The sources of greatest importance to the average physician are the exhaust gases of motor cars and illuminating gas. The exhaust gas of a gasoline motor contains about 6 per cent of CO when the motor is fairly well adjusted and if the mixture is excessively rich in gasoline the proportion of CO will be higher than this. The illuminating gas manufactured in large cities usually contains about 30 to 40 per cent of CO, but the gas obtained as a by-product of the manufacture of coke contains only about 10 per cent CO and natural gas contains almost none.

Peculiarities of Poisoning by Carbon Monoxide.—The symptoms of monoxide poisoning are the usual symptoms of anoxia (page 677). One of the outstanding symptoms is headache—a severe, throbbing, frontal pain, worse in the recumbent than in the upright position, accompanied by nausea and associated with decreased mental capacity. Peters and Van Slyke[126] suggest that this symptom may be due to an increase in cerebrospinal fluid pressure

consequent upon increased permeability of cerebral capillaries as a result of anoxia. Respiration is not stimulated as much as in most other types of anoxia because in this case the oxygen tension of arterial blood is normal (until breathing becomes insufficient) and the receptors of the carotid bodies and aorta are therefore not stimulated even though the quantity of oxygen available to the tissues is greatly reduced.* Fainting and collapse occur frequently, and if the heart is at all weak it is likely to be seriously affected. *When half the hemoglobin is combined with monoxide the subject is on the verge of unconsciousness and collapse and will probably die if the exposure continues.* This is in striking contrast with the effects of reduction to the same extent in the amount of hemoglobin in anemia, for patients with a hemoglobin content of 50 per cent are in no immediate danger from anoxia. As already mentioned, this is because monoxide has a double effect on the ability of the blood to yield oxygen to the tissues: it reduces the amount of oxygen carried by the blood to the extent that the hemoglobin is combined with CO, while at the same time the presence of carboxyhemoglobin increases the firmness of the combination of oxygen with the rest of the hemoglobin, so that it gives up its oxygen to the tissues only at an excessively low oxygen tension. The second of these influences is added to the first and is almost as strong, so that the anoxia produced by monoxide is nearly twice as severe as would be expected from the reduction in the amount of oxyhemoglobin alone; *the oxygen tension of venous blood in monoxide poisoning is only about half that usually seen in blood containing the same amount of reduced hemoglobin.* Monoxide can exert a depressant effect on tissue oxidations because it interferes with the

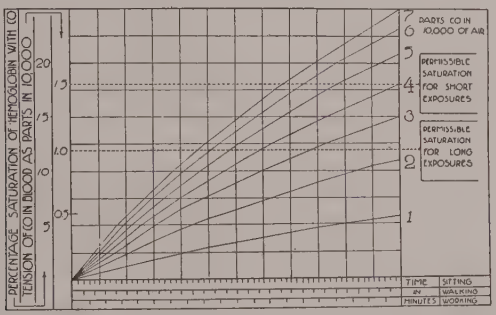

PERCENTAGE SATURATION OF HEMOGLOBIN WITH CO
TENSION OF CO IN BLOOD AS PARTS IN 10,000
PARTS CO IN 10,000 OF AIR
PERMISSIBLE SATURATION FOR SHORT EXPOSURES
PERMISSIBLE SATURATION FOR LONG EXPOSURES
TIME IN MINUTES
SITTING
WALKING
WORKING

Fig. 271.—Rate of absorption of carbon monoxide by the blood in persons exposed to concentrations up to 7 parts of CO in 10,000 of air for periods up to one hour, during rest (sitting) and for shorter periods of walking and working. (From Henderson, Haggard, Teague, Prince and Wunderlich: J. Indust. Hyg. 3: 79, 1921-22.)

activity of some of the enzymes concerned in the process (see Chapter XLVII), but this does not occur unless the concentration of CO is about one thousand times as great as that which suffices to cause death from combination of the gas with the hemoglobin; this effect of monoxide on tissue oxidations is an interesting fact, but it plays no part whatever in monoxide poisoning of higher animals or man.

*The reasons for this are as follows: (1) The amounts of CO in the inspired air which suffice to cause severe or fatal poisoning are of the order of 0.1 to 0.3 per cent (see Fig. 271), which are too small to produce a significant decrease in the partial pressure of oxygen in the alveolar air. (2) Monoxide does not directly interfere with the diffusion of oxygen across the pulmonary membranes, with the circulation in the alveolar capillaries, or with the solubility of oxygen in the blood. For these reasons the tension of oxygen in the arterial blood and the amount of oxygen carried by it in physical solution are not appreciably reduced in ordinary cases of monoxide poisoning as long as respiration continues to be adequate. (3) The hyperpnea of oxygen-lack is due mainly if not exclusively to reflexes aroused in the carotid and aortic bodies. These structures receive arterial blood directly through an artery arising from the occipital or external carotid and the aorta respectively. This blood is not exposed to any other active tissue before it reaches the chemoreceptors; the mass of tissue is so small that the amount of oxygen required to satisfy its needs must be very small, and the gas normally carried in physical solution in the blood is doubtless more than sufficient as long as the tension is not reduced. (4) When the amount of CO in the inspired air is high enough to reduce appreciably the partial pressure of oxygen in it (i.e., 5 per cent CO or more) the tension of oxygen in the arterial blood would of course be reduced, but in this respect CO is simply behaving like an inert gas and anoxic anoxia is superimposed upon the anemic anoxia that is the characteristic effect of this gas. Concentrations of this order are rarely encountered.

The severity of the symptoms depends on the amount of hemoglobin occupied by CO, and therefore on the tension of the gas in the alveolar air (also on the duration of the exposure—see below). *Since CO has an affinity 210 times that of O_2 for human hemoglobin a concentration of CO $\frac{1}{210}$ times that of O_2 in the inspired air would lead to 50 per cent saturation of hemoglobin with each gas; this would be accomplished by $\frac{20.9}{210} = 0.10$ per cent CO, or 10 parts per 10,000, which is dangerous to life if inhaled for a sufficient time.* Smaller concentrations (between 0.02 and 0.07 per cent) produce less characteristic effects, but prolonged exposure is liable to lead to symptoms of chronic anoxia (headache, nausea, weakness, etc.). Concentrations lower than 0.02 per cent (2 parts per 10,000) are harmless.

The duration of the exposure to monoxide is just as important as the tension of the gas in the inspired air unless the latter is so high as to produce instantaneous effects, which is rarely the case. Only about half the monoxide taken into the lungs is absorbed by the blood. Assuming 50 per cent saturation of hemoglobin by CO as the point at which collapse is likely to occur and absorption of half the CO in the inspired air, and knowing that the hemoglobin of an adult man can combine with about 1000 ml. of either CO or O_2 when fully saturated with either gas, we can estimate that the *average resting man is in danger of collapse when he has breathed enough air to contain about 1 liter of CO* (Peters and Van Slyke[126]). Henderson and his co-workers,[77] who made extensive experiments on men to ascertain the requirements for ventilation of the vehicular tunnel under the Hudson River between Jersey City and New York, came to the conclusion that *when the product (hours of exposure) × (concentration of CO in parts per 10,000 in the inspired air) = less than 6 in the resting subject there is no perceptible effect. When it reaches 9, headache and nausea appear. When it reaches 15 there is danger to life.* Thus exposure to 0.075 per cent CO for two hours, to 0.15 per cent for one hour, or to 0.3 per cent for one-half hour would be equally dangerous. The time of exposure is just as important as the concentration of CO in the air.

Exercise in the presence of monoxide is doubly dangerous, first because it increases the consumption of oxygen, and second because it leads to greater ventilation of the alveoli and therefore to more rapid absorption of the gas. A man who is exercising is in danger of collapse when his blood is only 30 per cent saturated with CO (compared with 50 per cent when at rest) and would therefore succumb to a CO concentration or a time of exposure about two-thirds that required to cause prostration of the resting subject. This is well shown in Fig. 271.

The after-effects of monoxide poisoning arise mainly from the central nervous system. One peculiar feature is that the symptoms may not come on until the subject has been removed from the noxious atmosphere and much of the poisonous gas has been eliminated from the body. An individual who has been poisoned by monoxide is not responsible for his actions; a man who had just been rescued from a mine shook hands with his rescuers and then knocked one of them down in resentment at the offer of further help. Collapse may occur several hours after the exposure, and there may be a prolonged period of mental aberration. Such individuals are unusually susceptible to respiratory diseases, and since their cooperation cannot be counted upon they must be watched and nursed carefully.

The treatment of acute monoxide poisoning follows the usual lines of resuscitation (page 667). Oxygen inhalation, with the addition of 5 to 7 per cent CO_2, is the most helpful procedure. *Chronic poisoning* with carbon monoxide is not generally recognized as a clinical entity, but it is possible that some vague symptoms, such as headache, nausea, and lassitude in workers in garages or foundries, or in children living in ill-ventilated quarters in which a gas stove is used, may be due to slow accumulation of the gas in the blood.

CHAPTER XLVI

THE EFFECTS OF BREATHING AIR UNDER INCREASED PRESSURE; AEROEMBOLISM; OXYGEN INHALATION; ARTIFICIAL RESPIRATION

CAISSON DISEASE

We have seen in Chapter XLV that when man breathes air under diminished pressure he develops a train of symptoms referable to the anoxemia which results from a decrease in the partial pressure of oxygen in the inspired air. When man exposes himself to air under *increased* pressure, another set of symptoms arise. These do not come on during the exposure to increased pressure but only afterward, when the victim has returned to more normal surroundings. They are ushered in and accompanied by severe pain and there is no acclimatization here as there is to low pressures. In these respects (as indeed in nearly all others) the physiological effects of exposure to excessive barometric pressures are quite different from those of exposure to subnormal pressures. The only outstanding similarity between the two is sudden collapse and death if the condition is extremely acute. Increased atmospheric pressures are encountered most frequently by divers and by workers in caissons; the symptoms are therefore widely known as "diver's palsy" and "caisson disease"; terms frequently used by the workers themselves are "the bends" and "the chokes." Recently, by reason of the advances in aeronautic engineering, occupants of aircraft have been exposed to precisely the same conditions because of the rapid rate of ascent of modern aircraft; for this the term "aeroembolism" has been suggested (see page 698). As we shall see when we come to inquire further into the symptoms, the underlying cause is the same in all these cases, i.e., embolization of blood vessels by bubbles of nitrogen which are liberated from solution in the body fluids by the reduction in tension of the gas in the blood. These emboli accumulate in the blood vessels because the rate at which nitrogen is liberated is faster than that at which the excess gas can be dissolved in the blood and eliminated in the lungs.

The *symptoms* are substantially the same no matter how the condition is brought about. Typically they begin with pains in the muscles and joints (usually the knees); the arthralgia may be due to distention of the joint by gas (which has actually been demonstrated roentgenologically in the knees of a victim of caisson disease[64]). Then come symptoms referable to emboli in the peripheral nerves, first sensory disturbances (formication, pruritus, localized sensations of heat and cold), then motor involvement (weakness, paralysis). Skin eruptions of the urticarial or herpetic type may occur at a rather early stage in the disease as encountered in aviators; these lesions apparently have a neurogenic origin. Involvement of the central nervous system may lead to vertigo, pains in the ears, and deafness, vomiting, breathlessness, convulsions, and coma. In severe cases there may be only a brief interval between the initial arthralgia and motor paralysis; the subject then becomes helpless and falls, and he is likely also to lose consciousness. Respiration becomes labored, the face is cyanotic, the pulse is almost imperceptible, and unless the victim is

quickly recompressed death is likely to ensue. In the milder cases recovery is usual but arthralgia and myalgia may persist for a considerable time.

Autopsies of persons dead of caisson disease have shown, as a rule, intense congestion of the viscera, hemorrhages into the spinal cord and brain, subcutaneous emphysema, and ecchymoses in the pleura and pericardium. In some cases interlobular emphysema of the lungs and laceration of the spinal cord and brain have been noted. In animals gas emboli are found in the blood vessels and the heart may be filled with froth instead of blood; this explains the weakness of the pulse in severe cases.

The Cause of the Symptoms.—For many years it has been known among divers and caissoniers that "on ne paie qu'en sortant,"[67] i.e., that the danger arises, not from the compression, but from the subsequent decompression. This was first established by the work of Paul Bert, which has been repeatedly confirmed (see Haldane[67]). The recent discovery that the disease can appear in its most severe form in an individual who has never been exposed to a pressure higher than that of the normal atmosphere, but who is decompressed by rapid ascent in an airplane, shows that the preliminary sojourn at the increased pressure is not essential. The aviator suffers because he is decompressed from a normal barometric pressure to a subnormal one, whereas the diver or caissonier shows identical effects on being decompressed from a hypernormal pressure to a normal one. Behnke[23] points out that an aviator ascending from sea level to an altitude of about 33,000 feet is being subjected to exactly the same degree of decompression as a diver coming to the surface after a sojourn at a depth of 100 feet in sea water; in the former case decompression occurs from the pressure of one atmosphere to one-quarter that value (see Table XXIV, page 679), while in the latter it occurs from a total pressure of four atmospheres to that of one.

The diver and caissonier are unavoidably exposed to increased pressure, the former because the air pressure inside his suit must be as high as that of the surrounding water or he would be unable to breathe, the latter because water is kept from flooding the excavation only by raising the pressure inside the latter. Every 33 feet of sea water (34 feet of fresh water) means an additional pressure of one atmosphere. The blood of the man exposed to an increased pressure takes up the gases of the atmosphere in direct proportion to their partial pressures (Henry's Law—page 616); at a pressure of two atmospheres, twice as much gas will be dissolved as at one. The only gases that we need consider are oxygen and nitrogen, since carbon dioxide is not (or should not be) allowed to accumulate because the resulting breathlessness will greatly impede the performance of work and CO_2 may (when compressed) cause stupefaction (i.e., narcosis). The excess oxygen is used by the tissues, but the body can do nothing with the excess nitrogen except dissolve it until the tension of the gas in the tissues, tissue fluids, and blood is again equal to that in the atmosphere (i.e., until saturation has occurred); then the number of gas molecules leaving the blood in the lungs is again equal to the number entering it (i.e., a new equilibrium is struck at a higher tension, involving the movement of more gas molecules in proportion to the increased pressure). Since nitrogen is an indifferent gas, no abnormalities result from the presence of increased amounts of it as long as it remains dissolved.

The peculiar dangers in this situation arise from two facts: (1) nitrogen diffuses relatively slowly through living membranes; (2) it is about five times as soluble in fat as in water,[160] and since fatty tissues are also rather poorly vascularized, equilibrium between blood and fat with respect to the tension of nitrogen is slowly attained in either direction. Consequently, it takes considerable time for the body to absorb its full quota of nitrogen at a given atmospheric pressure and to eliminate the excess when decompression occurs. The blood in man constitutes one-twentieth of the body weight, so that if the tissues were all liquid, they would dissolve 20 times as much nitrogen as the blood. Because of their fat content, however, the tissues take up more than this, the amount in

the average man being about 35 times as much as the blood. Since a complete round of the circulation takes about one minute, the body, when suddenly exposed to an increased pressure, will be about $\frac{1}{35}$ saturated with nitrogen in one minute, another $\frac{1}{35}$ in two minutes, and so on. At this rate the body would be about 22 per cent saturated with nitrogen in five minutes and about half saturated in twenty-five minutes, but it would take about two hours for saturation to be complete, even if the blood were evenly distributed throughout the body. Because of the poor vascularization of fatty tissues these will lag behind the others and complete saturation will be further delayed.

The results of sudden decompression of the body are entirely comparable with those of sudden removal of the stopper from a bottle of carbonated fluid: the gas, previously dissolved at a high pressure and entirely invisible, comes out of solution in gross bubbles and effervescence occurs. To decompress without danger involves the counterpart of making a tiny hole in the stopper: the excess gas escapes gradually and no effervescence results. Other things being equal, it takes about as many minutes to desaturate as to saturate. Both processes can be accelerated by exercising, and for two reasons: first, because the circulation rate and alveolar ventilation are both increased; and second, because the blood flow through the tissues is accelerated by the vasodilatation attendant on muscular exercise. This fact has long been utilized by divers and caissoniers, who can hasten materially the rate of decompression by exercising or working during the process. Perhaps it could also be utilized by the occupants of a rapidly ascending aircraft.

When decompression is rapid, the excess nitrogen dissolved in the blood at the higher pressure comes out of solution and gas emboli may be formed at once in the pulmonary capillaries (hence the asphyxial symptoms). Because of the lowered pressure of nitrogen in the blood, bubbles of the gas also appear in the tissues, first in those with the best blood supply, later in those with poorer vascularization. Myalgias and epigastric pain are probably due to embolization of blood vessels in the muscles and gastrointestinal tract, the arthralgias to distention of the joints with gas liberated into them, and the nervous symptoms to gas emboli in vessels supplying the central and peripheral nervous systems. Once these emboli have appeared they can be gotten rid of rapidly only by bringing them back into solution by raising the atmospheric pressure again.

The Prevention of the Symptoms.—From what has been said about the cause of these symptoms it follows that, if they are to be prevented, decompression must take place so gradually that the excess nitrogen can be eliminated from the body rapidly enough to prevent the appearance of gross bubbles of nitrogen in the capillaries. The time required will depend both on the extent of the original compression (in a diver or caisson worker) and on the duration of the exposure. In the *aviator* the extent of the compression is of course always the same (i.e., equilibrium at a normal barometric pressure); the important factors here are the rate and extent of decompression. Experience has led to the establishment of certain rules for the decompression of divers and caisson workers.[67, 83] The corresponding situation in aviators is too recent to permit similar treatment (see Armstrong[7]). In any case, once serious symptoms have appeared, immediate recompression is indicated.

Recently helium has been substituted for nitrogen in the air used to supply divers in the U. S. Navy, and this has made possible deeper dives, longer sojourn under water, and more rapid ascent without dangerous symptoms. The reason for this is that helium is only about one-half as soluble as nitrogen in body tissues while at the same time it diffuses about twice as rapidly as nitrogen through living membranes. Consequently, the amount of helium taken up in the diver's body in a given time and at a given pressure would be considerably less than the amount of nitrogen absorbed under the same conditions; the rate at which the excess helium is eliminated from the body when decompression takes place is also considerably more rapid than would be the case in a nitrogen-oxygen atmosphere. The fact that helium is so much lighter than nitrogen that a helium-oxygen atmosphere can be moved with less effort and will more

readily pass a partial respiratory obstruction plays no part in this particular use of the gas; it is important in the relief of asthma, laryngeal obstruction, tracheal stenosis, etc. (Barach[11]).

AEROEMBOLISM

If it is true that the deleterious effects of exposure to air under increased pressure are due to obstruction of capillaries by bubbles of nitrogen which are no longer held in solution when the environmental pressure is rapidly reduced from an abnormally high level to that of the normal atmosphere, it follows that similar effects should be elicited by the sudden reduction in the environmental pressure encountered during rapid ascent in an airplane. It is now well known[8, 155] that this is the case and Armstrong[8] has suggested the term *aeroembolism* to designate the pathological entity thus brought about. The symptoms are identical with those of caisson disease: pain in the joints usually is the first sign, followed by paresthesias (formication, pruritus, or localized sensations of heat or cold) and these by symptoms referable to gas emboli in peripheral nerves, or in the central nervous system (paralyses, convulsions, coma). Skin eruptions of the urticarial or herpetic type may occur at a rather early stage.

The *cause of the symptoms* is obviously occlusion of end-arteries by bubbles of nitrogen, the rate of diminution in the environmental pressure having been too rapid to permit the gas to be eliminated by the lungs as rapidly as it comes out of solution in the body fluids. According to Armstrong, these effects are not likely to arise at any level lower than 30,000 feet (226 mm. barometric pressure) no matter how rapid the ascent; at or above that level, however, symptoms may ensue even when the rate of climb is less than 200 feet per minute. Different individuals vary greatly in their susceptibility to this condition but here, as in divers and caissoniers, fat subjects are generally more susceptible than lean ones, and for the same reason in both cases, viz., nitrogen is much more soluble in fat than in water and desaturation of fatty tissues is a very slow process because of their poor blood supply. In some persons the symptoms come on at an altitude considerably below 30,000 feet. As in caisson disease, the symptoms begin only after the exposure has lasted for some time; this delay tends to be greater with slower rates of ascent than with more rapid ones.

The *treatment of aeroembolism* is obviously recompression, which is easily done simply by descending to a lower altitude. This condition must not be confused with the anoxia of high altitudes although some of the outstanding effects (especially those on the central nervous system) are very similar. Oxygen inhalation will not remedy aeroembolism once it is established; it will aid in ridding the body of nitrogen because it lowers the tension of the latter gas in the inspired air, but existing gas emboli can be gotten rid of rapidly only by redissolving them, and this necessitates a return to the pressure at which they go into solution. Oxygen inhalation would prevent aeroembolism provided that sufficient time is given for desaturation with nitrogen to occur; if the ascent is to be rapid (and most of the modern military aircraft can climb much faster than is necessary to lead to aeroembolism) it will, however, be necessary for the inhalation to begin some time before the ascent. Because 30,000 feet appears to be a critical level for the occurrence of aeroembolism in many persons it is probably inadvisable for commercial aircraft to operate

as high as this even with sealed cabins; in the event of sudden leakage or failure of the compressing mechanism oxygen inhalations could be used to forestall fulminating anoxia, but they would not prevent severe or fatal effects from the gas emboli resulting from rapid decompression. Helium-oxygen mixtures could be used to prevent aeroembolism in aviators as well as "the bends" in rapidly decompressed divers, but this procedure, while entirely practical for diving because special vessels are outfitted for the purpose, is impractical in aircraft because it would involve additional equipment and offer slight if any advantages over inhalation of oxygen alone.

Since the boiling point of water is reduced by lowering the barometric pressure to which it is exposed, an altitude must exist at which the body fluids would boil at body temperature. Theoretically this should occur at an altitude of 63,000 feet, for here the barometric pressure (47 mm. Hg) is equal to the water vapor tension of the body fluids (page 548). Armstrong and his colleagues[8] have actually seen this phenomenon taking place in a transparent cell through which an animal's blood was passed. No changes were visible until an altitude of 55,000 feet was reached, when the film of blood suddenly assumed a grayish appearance, probably because of the liberation of minute bubbles of gas or vapor. At 58,000 feet macroscopic bubbles appeared, at 61,000 these were more numerous, and at 63,000 very suddenly all of the fluid blood was replaced by a mass of bubbles. This phenomenon is interesting, but since the occupants of an open-cockpit plane would die from anoxia at a considerably lower altitude even if they were breathing 100 per cent oxygen (page 703) the practical importance is not great.

THE THERAPEUTIC VALUE OF OXYGEN

When oxygen is properly administered in certain types of pulmonary disease before the patient has become moribund, very great benefit may result from the treatment, and as far as can be told a fatal termination is often averted.

Theoretical Considerations.—In order to understand the physiological principles involved in this treatment, it is important to remember that although more than fifty times as much oxygen is combined with hemoglobin as is in simple solution in the blood plasma, yet it is the latter which really diffuses into the tissues. The pressure of oxygen in the plasma, in other words, the diffusion pressure of oxygen, is the determining factor in causing it to permeate the tissues, and whenever this pressure begins to fall under normal conditions, more is added to the plasma by dissociation from the oxyhemoglobin of the corpuscles. The plasma retails the oxygen to the tissues, and the corpuscles are the wholesale warehouses from which the plasma replenishes its stock. The unloading of oxygen from the oxyhemoglobin to the plasma is assisted by various chemical changes that take place while the blood is in the capillaries. From these considerations it follows that an efficient supply of oxygen to the tissues could be maintained without any hemoglobin if we were to put an excess of the gas into simple solution in the plasma; that is, if enough were forced into solution in the plasma in the lungs so that the tissue requirements could be met without any local addition from oxyhemoglobin. Two experiments may be quoted to show that it is possible to fulfill these conditions:

1. After replacing all the blood from the blood vessels of a frog by artificial plasma (Ringer's solution) the animal can be kept alive for days in a vessel

containing pure oxygen (i.e., five times the amount present in air) and during this time the O_2 consumption and CO_2 production are practically the same as under normal conditions.

2. Small mammals (mice) exposed to air containing more than 0.5 per cent of carbon monoxide (contained in coal gas) soon become moribund, because the oxygen carrying power of the hemoglobin is entirely abolished by the formation of carboxyhemoglobin. If the animals are now transferred to pure oxygen under two atmospheres pressure (i.e., ten times the amount in air) they quickly recover.

Both experiments show clearly that if we succeed in getting sufficient oxygen into simple solution in the plasma, the oxyhemoglobin is not necessary to supply the tissues with this gas.

One of the greatest uses of oxygen inhalation is in the *treatment of poisoning by carbon monoxide.* In this condition the monoxide competes with oxygen for combination with the iron of the hemoglobin molecule and the affinity of the former is about 210 times that of the latter. Yet it is a quantitative relationship, and as the tension of oxygen is increased this gas displaces monoxide. The addition of CO_2 to the inspired mixture assists in turning monoxide out of the blood for two reasons: (1) The deeper breathing leads to an increase in the tension of oxygen in the alveoli while at the same time the monoxide is more thoroughly removed; (2) CO_2 affects the dissociation curve of carboxyhemoglobin in the same way as it does that of oxyhemoglobin (page 632); therefore at a given tension of monoxide in the alveolar air less is combined with hemoglobin when the CO_2 tension is increased. In addition, the inhalation of pure oxygen leads to the uptake of more oxygen in physical solution (2 ml. per 100 from an atmosphere consisting entirely of oxygen instead of 0.3 ml. from the normal atmosphere), and that fraction of hemoglobin which normally passes through the lungs unoxygenated (equivalent to about 1 ml. of oxygen per 100 ml. of blood) is oxygenated; thus the blood takes up an additional load of about 3 ml. of oxygen per 100 in forms readily available for utilization by the tissues and the acute symptoms of anoxia can therefore be immediately alleviated by inhalation of pure oxygen even without displacement of CO from its combination with hemoglobin.

In pulmonary edema, in "gassed" cases, in bronchitis, and in decompensated cardiac cases, oxygen is of undoubted value, when it is properly administered. Many cases of *pneumonia* are also benefited by such treatment, but there are others in which the heart is so profoundly affected by toxic substances that oxygen may perhaps be of little use. Evidence of this benefit is afforded by the easier and deeper breathing, the slowing of the pulse, the disappearance of cyanosis and the greater ease and comfort experienced by the patient. Not only do these effects persist as long as the gas is given, and thereby serve to tide over a crisis and permit the natural defensive agencies of the body more successfully to combat the abnormal condition, but they often outlast the administration. In severe angina pectoris associated with coronary occlusion oxygen inhalation may bring relief from pain because it ameliorates the anoxia of heart muscle that was responsible for the pain.[26]

Quantitative evidence that in pneumonia the arterial blood is improperly saturated with oxygen in proportion to the degree of cyanosis, and therefore of the condition of the patient, has been furnished by Stadie.[152] In a normal person the arterial blood carries 95 per cent of its full load of oxygen, but in pneumonia only a little over 80 per cent. Meakins[114]

has confirmed these findings, and has added most important observations on the effect of oxygen inhalations by the Haldane method. In a case of pneumonia the oxygen unsaturation on the eighth day of the disease was 17.9 per cent. After two hours of oxygen treatment (at a rate of delivery of 2.5 liters O_2 per minute) the unsaturation percentage fell to 9.08, and after 18 hours (at 1 liter per minute) it was 9.0. The O_2 was then discontinued and in 4 hours the unsaturation percentage had risen to 15.5. It fell subsequently to 3.05 after 24 hours, during which 3 liters O_2 per minute was administered. Shortly after this the crisis occurred. Similar results were obtained in a case of chronic bronchitis, and even in normal men it was found that inspiration of 3 liters of O_2 per minute for 100 minutes changed the arterial blood from 4.4 per cent unsaturation to 1.87 per cent.

To explain exactly how the oxygen acts in this group of cases several possibilities must be considered. In the first place we must suppose that the respiratory membrane has become greatly reduced in extent because the alveoli in certain parts of the lungs have become more or less filled with fluid or exudate. Under these circumstances the blood circulating in the vessels of the affected portion of lung cannot be reached by a sufficient amount of oxygen to saturate its hemoglobin fully, because there is an inadequate diffusion pressure of oxygen to penetrate the thick layer of fluid between the alveolar air and blood. When the exudation completely fills the alveoli the blood ceases to circulate through the capillaries of the affected part, so that all the blood is passing through the capillaries of healthy parts. This explains why the arterial blood may remain bright red in color in cases where there is complete consolidation or collapse of considerable areas of lung. So long as the hemoglobin is not fully saturated the tension of oxygen in the plasma must become very low and little can be available for the tissues when the blood arrives in their capillaries. When excess oxygen is breathed, the amount which goes into solution in the fluid will become proportionately raised so that there will be a much better chance for a sufficient amount to reach the plasma, so as to saturate the hemoglobin and create a proper tension in the plasma.

In pneumonia the blood which leaves the lungs as a whole is a mixture of blood, still more or less venous from the blocked portions, and of arterial blood from the healthy portions, and it may be considered that the mixture is just on the border line of being adequate to supply the oxygen requirements of the tissues and nerve centers—otherwise the individual could not live. A very small improvement in the oxygen supply will therefore suffice to turn the tide. It is possible that the additional oxygen may reach the blood by diffusion through the fluid that has collected in the alveoli. By increasing the pressure of oxygen in the inspired air, more will become dissolved in the fluid (by Henry's Law, page 616) so that the pressure gradient from air to blood through the fluid will become steeper. But another factor must be considered; namely, that the increased partial pressure in the healthy alveoli has caused more O_2 to go into simple solution in the plasma of the blood circulating in these portions, and although this cannot cause the hemoglobin of the blood to carry away any greater load of the gas, yet when this blood is mixed with that from the pathological lobes, the dissolved oxygen will assist in bringing the hemoglobin up to its proper degree of saturation with oxygen.

It has been imagined by some that it is useless to give oxygen because the dissociation curve of the blood at varying pressures of the gas (page 632) shows that even after reducing the partial pressure of oxygen to one-half that obtaining in normal alveolar air, the blood still takes up 80 per cent of its full load. It is argued that it is therefore futile to attempt to increase the oxygen carried by the blood by raising the partial pressure in the air which is inspired into the still healthy alveoli. From what has been said above, however, it is clear that this viewpoint does not take into account two important effects which follow when the partial pressure of the oxygen is increased; namely, that under this condition oxygen diffuses much more rapidly through the fluid in the pathological

portions of the lung, and that at the same time more goes into simple solution in the plasma that is circulating in the healthy portions.

Principles in Method of Administration.—The success of any treatment with oxygen must depend on several factors, the most important of which are: (1) to get as much of the gas into the alveoli as possible; (2) to start the treatment early before irreparable damage has been done because of anoxemia; and (3) to maintain the administration until cyanosis disappears. With regard to the first of these factors, it has sometimes been thought that there is an element of danger in giving too much oxygen. This depends on the observation made by several investigators that animals that have been caused to live in more than one atmosphere of the pure gas for some time develop symptoms of pulmonary irritation, which may lead to pneumonia. By the best methods of administration, however, a concentration of not more than 85 per cent of oxygen can be attained in the alveoli. Karsner has shown that under such conditions there is no danger in inhaling pure oxygen, even for long periods of time.

The importance of early administration is evident when we realize that injury to the nerve centers and the tissues from insufficient oxygen usually develops insidiously, and that once started the damage must lead to a progressive deterioration of the vital functions of the body. The respiratory center is among the first to suffer from the anoxemia. The result is shallow and rapid breathing. Such breathing does not, however, properly ventilate the alveoli, so that the anoxemia becomes aggravated, and a vicious respiratory circle becomes established. The defensive agencies of the body against toxins and bacteria are also depressed by the anoxemia so that resistance to the further progress of the disease is lessened. It is also possible that prolonged oxygen deficiency, or the appearance of some toxic substance in the blood as a result of anoxia, renders the hemoglobin less capable of carrying oxygen by changing some of it into methemoglobin. It is at least significant that this compound is formed in animals after massive injections of streptococci (Peabody[123]). The maintenance of an adequate tension of oxygen in the plasma by administration of oxygen may retard the development of toxic substances.

For similar reasons, the administration should be maintained until all signs of deficient oxidation are removed, the best index of this being the color of the face. So long as there is any anoxemia the face has a characteristic pale ashen hue, different from that of ordinary capillary congestion.

Methods of Administration.—It may be said at once that the older clinical practice of placing a funnel connected with an oxygen tank in front of the patient's face is seldom of any use. At the rate at which the oxygen is usually applied by this method, it is inconceivable that any measurable increase in the percentage of oxygen in the alveolar air could be attained, and if enough gas were turned on to have some influence, the waste due to diffusion into the air would be tremendous.

Where no special apparatus is obtainable for the administration, the best method is to pass a wide gum elastic catheter into one nostril, through which the gas, after bubbling through water in a flask, is passed as rapidly as is comfortable for the patient. The method is rendered much more efficient if the open nostril is closed by the attendant during each inspiratory act. It has been found that by this latter procedure the concentration of oxygen in the alveolar air can be raised to 35 per cent. With the opposite nostril open, this percentage was much less. A smaller catheter passed through one nostril into the nasopharynx is even more effective.

Of the special appliances now available, the most satisfactory is the face mask devised by Boothby and his colleagues and commonly known as the BLB mask.[102] This is also the most effective method for administering oxygen to occupants of aircraft. The oxygen content of the inspired air in this apparatus can be raised to 80-100 per cent. It is, however, rather uncomfortable to use for long periods. The same workers[27] have also devised a small, self-contained inhaler and source of oxygen for use by aviators in the event of sudden failure of the plane's oxygen supply, or of the necessity to "bail out" at a high altitude. They point out that under either of these conditions, without any emergency supply of oxygen, it would be necessary to plunge to a level of breathable air (18,000-20,000 feet) in about one and one-half minute or consciousness would be lost; if the plane was at 35,000 feet when this happened, the strain of such a plunge on machine or man would be terrific and perhaps unbearable.

The various forms of oxygen tents cannot raise the oxygen content of the inspired air much above 40-60 per cent.

Administration of oxygen through a tracheal catheter has already been mentioned (page 672); by this means anoxemia can be prevented in the absence of any respiratory movements. It is also said to be effective in newborn infants even though the lungs have never been expanded (page 674).

Limitations of Oxygen in Aviation.—At first glance it might seem that the height at which safe flight is possible for subjects breathing pure oxygen is limited only by the capacity of the aircraft. Unfortunately this is not the case, and since the reasons are not yet well known, it is proper to inquire briefly into them at this time. The reader who is particularly interested will find the subject discussed fully by Armstrong.[8]

As far as respiration is concerned, the main physiological limitations to ascent in aircraft are: (1) the danger of aeroembolism consequent upon rapid ascent, and (2) the danger of anoxia resulting from reduction in the barometric pressure until the tension of oxygen in the inspired air becomes too small to secure adequate oxygenation of the blood in the lungs; this can occur even

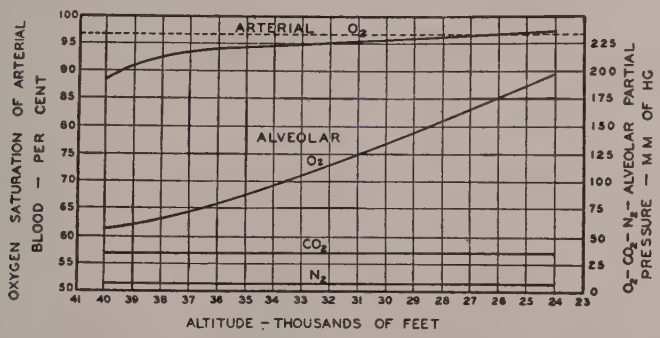

OXYGEN SATURATION OF ARTERIAL BLOOD — PER CENT
ARTERIAL O_2
ALVEOLAR
O_2
CO_2
N_2
O_2 — CO_2 — N_2 — ALVEOLAR PARTIAL PRESSURE — MM OF HG
ALTITUDE — THOUSANDS OF FEET

Fig. 272.—Oxygen, carbon dioxide, and nitrogen tensions in alveolar air and oxygen saturation of arterial blood while breathing pure oxygen at altitudes between 24,000 and 40,000 feet. Average values obtained on healthy young subjects. (From Armstrong: Principles and Practice of Aviation Medicine, Baltimore, 1939, Williams and Wilkins.)

though the inspired atmosphere consists entirely of oxygen. The first of these has already been considered (page 698); inhalation of oxygen will not obviate aeroembolism unless begun some time before the ascent. The second has been investigated by Armstrong and Heim,[8] with results that are shown in Fig. 272.

These subjects were studied while breathing practically 100 per cent oxygen at altitudes ranging from 24,000 to 40,000 feet. At the former altitude the alveolar air showed the following average tensions: oxygen 195 mm., nitrogen 5 mm., carbon dioxide 36 mm.; the arterial blood was a little closer to complete saturation with oxygen at the 195 mm. tension than it was in the same subjects breathing ordinary air at sea level. Both alveolar oxygen tension and arterial oxygen saturation fell steadily as the altitude increased, and at 33,000 feet the former reached 105 mm. (which is practically a normal value for the alveolar oxygen tension at sea level). Arterial oxygen saturation began to fall below its sea level value at about 27,000 feet, and at 33,000 feet it was about 94.5 per cent as compared with a normal of 97; the reason for this fall in spite of a supposedly normal alveolar oxygen tension is as yet unknown.

At 40,000 feet alveolar oxygen tension had fallen to 62 mm. and arterial saturation to 88 per cent (average); the latter corresponds approximately with the value found when breathing ordinary air at 12,000 feet. Some of these individuals did not show a significant hyperpnea as anoxemia developed, and in these the arterial oxygen saturation fell to 83 per cent at 40,000 feet; this is about the same as that found when air is breathed at 15,000 feet (see Table XXIV, page 679).

"From the practical standpoint, taking into consideration not only our ability to create normal concentrations of oxygen in the lungs, but also the limitations of our present oxygen equipment, the frailties of human nature, and the consequences of a loss of oxygen supply at high altitude, it is believed that it cannot be considered a safe practice to fly above 20,000 feet where the safety of the flight depends on the inhalation of oxygen. Flights at 25,000 feet must be considered as definitely hazardous and 30,000 feet should be the absolute allowable limit of high flying in any except the most unusual circumstances. In no instance should anyone ever be allowed to fly above 40,000 feet" (Armstrong,[8] p. 321). The absolute ceiling to flight with oxygen (but without compression of the inspired gas) is reached when the barometric pressure equals the sum of the exhaled water vapor (tension 47 mm.) and carbon dioxide (tension 40 mm.); this is encountered at an altitude of about 50,000 feet (Table XXIV). At this height the alveolar oxygen tension would be zero even if pure oxygen were being inhaled, for the lungs would be filled with water vapor and carbon dioxide (total tension 87 mm.) and the pressure exerted on the inspired oxygen (87 mm.) could not force it into the deeper air passages. It is true that the carbon dioxide tension should be reduced below the value that is normal at sea level (40 mm.) by the increased respiration characteristic of high altitudes and this would raise the absolute ceiling somewhat; yet even if there were no carbon dioxide whatever in the alveoli (which could not occur) the exhaled water vapor alone, as we have seen on page 699, would fill the lungs completely at an altitude of a little less than 63,000 feet. Armstrong[8] found that rabbits exposed while breathing pure oxygen to altitudes of 43,000, 45,000, 47,000 and 50,000 feet died from anoxia in 120, 32, 7, and 3 minutes respectively.

These limitations can of course be circumvented by means of a sealed-cabin airplane in which the occupants breathe air that is maintained at a pressure approaching the normal at sea level. In so doing, however, another hazard—that of aeroembolism—is encountered at altitudes higher than 30,000 feet (page 698).

Oxygen Poisoning.—Since it is now possible by means of suitable equipment (such as the BLB mask[102]) to inhale practically 100 per cent oxygen for indefinite periods of time, the possibility of toxic effects from this procedure becames a matter of considerable importance. Recent investigations indicate that inhalation of pure oxygen by normal persons at sea level should not be continued for longer periods than six to seven hours because, after that time, symptoms suggesting pulmonary irritation (substernal soreness aggravated by a deep inspiration) and hyperactivity of the parasympathetic nervous system (flushing of the face, nausea, or actual vomiting) are apt to appear;[23] in one case repeated vomiting and actual bronchopneumonia ensued.[22] Pure oxygen given under increased pressure produces epileptiform convulsions; at a pressure of 4 atmospheres these come on in about forty-five minutes and Behnke[23] has suggested that the convulsions so produced might be tried in the treatment of

mental diseases. The cause of these symptoms is at present uncertain; direct irritation of the respiratory passages and lungs probably accounts for the pulmonary symptoms, but the other manifestations remain unexplained. The convulsions have been attributed to accumulation of carbon dioxide in nerve cells because, since the needs of the tissues for oxygen are met by the amounts physically dissolved in the plasma at such tensions as these, oxyhemoglobin is not reduced and alkali is not made available to transport carbon dioxide away from the tissues. If this explanation is correct, the CO_2 tension of the venous blood should be higher than normal under such circumstances, but this apparently is not the case; furthermore, there is abundant evidence to indicate that carbon dioxide in excessive amounts is narcotic to nerve cells but little or none to justify the belief that it is a convulsant.

The significance of these facts for the average physician is probably not very great for several reasons: first, there is general agreement that inhalation of oxygen in concentrations lower than 60 per cent is entirely harmless under any circumstances, and as the gas is usually given this concentration is not likely to be exceeded; second, when used by aviators the inhalation would not begin until an altitude was reached at which even 100 per cent oxygen would produce a tension in the blood little if at all above that normally existing while breathing air at sea level; third, in patients in whom inhalation of pure oxygen is indicated (such as cases of severe poisoning by carbon monoxide, coronary occlusion with severe shock, pneumonia, or acute pulmonary edema) the risk of doing harm by means of the oxygen is trivial compared with the damage being done by anoxia. It is not unlikely that patients with severe anoxia are less likely to be poisoned by oxygen than are normal subjects.

ARTIFICIAL RESPIRATION

By far the most satisfactory method to use in the resuscitation of asphyxiated persons is that known as Schäfer's. The patient is placed in the prone position with the arms extended and the head turned to one side. The mouth and throat are cleared of any foreign material and the tongue is pulled forward. The operator kneels astride the patient and places his open hands over the lower ribs with his arms extended. He then leans forward so as to compress the abdomen and force the diaphragm upward, maintaining the pressure for about two seconds, and follows this by leaning back to release the pressure, again for about two seconds. This is kept up until natural breathing returns or until it becomes certain that success is impossible. It has been shown by measurement of the air entering and leaving the lungs that this is by far the most efficient method of resuscitation, but its efficacy depends on seeing (1) that the pressure is applied to the lower ribs and (2) that the rhythm is not made too rapid.

When available, inhalation through a mask applied over the patient's face of oxygen containing 7 per cent CO_2 is of very great advantage. The oxygen tension is thereby greatly raised in the blood, improving the heart's action, and the CO_2 acts as a stimulus to the respiratory center. In CO-poisoning the use of O_2 and CO_2 is especially important. In all cases the patient must, of course, be kept warm by hot water bottles, etc.

The most efficient method of artificial respiration (and the only one which can be kept in operation for long periods of time in patients who are unable to

breathe) is the Drinker respirator.[50] This is a metal chamber in which the body of the patient is placed while the head remains outside; a rubber collar about the neck provides an air-tight seal. By means of mechanical pumps air can be rhythmically sucked out of the chamber and both the rate and the intensity of the process can be regulated. Thus the chest is expanded because the pressure on its surface is reduced; the head is outside the chamber and air under atmospheric pressure enters the lungs for the same reason that it does when the subject breathes naturally; i.e., because the pressure on the pleural surfaces of the lungs is lower than atmospheric. The expiratory phase of breathing can be allowed to occur passively or it can be made active—the latter by pumping air under positive pressure into the chamber during the expiratory part of the cycle. This apparatus is available in a number of large hospitals in the United States and it has proved to be extremely satisfactory for both acute and chronic cases.

Methods of artificial respiration which depend upon blowing air under positive pressure into the lungs have fallen into disrepute. One reason for this is that if the blast of air (or oxygen) is sufficient to distend the chest it may at the same time press upon the walls of the alveoli with enough force to obstruct the flow of blood in the pulmonary capillaries. The ventilation of the alveoli is accomplished with little or no change in their size (page 618) and therefore without interference with the pulmonary circulation, but the introduction of positive pressure in the respiratory passages alters this situation in a most dangerous way. The manual methods (such as that of Schäfer) and the Drinker apparatus obviate this danger. Yet the method of intratracheal insufflation (page 668) of oxygen can be very satisfactory if the pressure of the gas is not allowed to become too high. The natural tendency in an emergency in which artificial breathing is necessary is to overdo the latter; with manual methods little harm can be done to the patient but with a blast of air or oxygen released into the trachea a great deal of harm can be done. With a mechanical device such as the Drinker respirator it is easily possible to overventilate the lungs, and it may even be possible to distend the alveoli sufficiently to interfere with the pulmonary circulation, particularly if air does not freely enter and leave the respiratory passages. It is probably always better to underventilate slightly than to overventilate when artificial respiration is applied by any method. We have already seen (page 674) that none of these methods can safely be used to expand the lungs of a newborn infant; perhaps the situation would be different if the bronchial muscle were first relaxed, but the reader should clearly understand that this remains to be proved.

CHAPTER XLVII

THE SUPPLY OF OXYGEN TO THE TISSUES

We are now ready to consider the uptake of oxygen by the tissues and the removal of CO_2 from them. As has been mentioned repeatedly in the preceding pages, this is the respiratory process which occurs in all forms of life except anaerobic organisms. The gas exchange in the lungs and the physicochemical equilibria concerned in the transport of the respiratory gases are undoubtedly important, but they are only the means whereby the respiration of the tissues is made possible. Cell respiration is the climax of the entire respiratory process. Since it lies at the basis of the energy changes of the body, cell respiration will be considered in the section devoted to the subject of metabolism (see the next chapter).

In our considerations of the regulation of respiration and of the maintenance of the reaction of the blood we have seen that CO_2 occupies a place of special importance, but tissue respiration deals almost exclusively with the supply and utilization of oxygen, and the removal of CO_2 is a factor of comparatively little moment. There are several reasons for this. One is that CO_2 diffuses so much more readily than oxygen that the former gas can escape from the body much more easily than the latter can enter it. Another is that the body has an abundance of mechanisms for compensating for increases in the amount or tension of CO_2, but it has no comparable means for protecting itself against decreases in the amount or tension of oxygen; there are no reservoirs or reserves of oxygen in the tissues. Finally, an increase in the amount of CO_2 in the tissues may narcotize them but it will not damage them, whereas anoxia, as we have already seen (page 666), "not only stops the machine but wrecks the machinery" (Haldane). The call of the tissues for oxygen is the most fundamental fact of the entire respiratory process.

The mechanisms involved in supplying oxygen to the tissues and removing carbon dioxide from them have already been considered for the most part, but repetition will not be amiss.

The arterial blood reaches the capillaries with the reaction $Hb + O_2 \rightleftharpoons HbO_2$ in equilibrium at an oxygen tension of 90 mm. and a CO_2 tension of 40 mm. The blood contains 20 ml. of oxygen per 100 ml. Of this about 0.3 ml. is in physical solution in the plasma. As long as the blood is in the thick-walled arteries and arterioles nothing can happen to disturb the equilibrium, but in the capillaries the plasma is separated from the tissue fluids only by the permeable endothelial wall. The tension of oxygen in the tissue fluids is lower than that in the plasma because oxygen is constantly diffusing from the former into the cells which utilize it. If the tissue is at rest the oxygen requirement is only that necessary to maintain the physiological structure (semipermeability, separation of constituents, etc.). A fair estimate of the oxygen tension in the fluid surrounding a tissue at rest is about 22 mm.,[132] which is a little lower than that of venous blood (40 mm.). When the blood reaches the capillaries the oxygen molecules pre-

viously held in the plasma under a tension of 90 mm. are forced through the capillary wall because the tension outside the wall is only 22 mm.; they reach the tissue fluid and move on to the tissue cells. The tension of oxygen in the plasma rapidly falls, and this immediately leads to a dissociation of oxygen from combination with hemoglobin. The oxygen molecules liberated from hemoglobin diffuse out of the erythrocytes into the plasma, and thence through the capillary wall. At the same time CO_2 diffuses into the blood because its tension in the tissue fluid is 45 mm. or more and in the arterial blood only 40 mm.; the hemoglobin becomes more acid and its ability to hold oxygen is therefore decreased, so that more oxygen molecules are made free to diffuse out into the plasma. By the time the blood traverses the capillaries and enters the veins it contains about 15 ml. of oxygen per 100 ml. and has an oxygen tension of about 40 mm. (i.e., the oxygen tension of venous blood is not quite as low as that of the tissue fluid, so that a continuous "suction" for oxygen exists). Although the arterial blood contains 20 ml. of oxygen per 100, only 5 ml. of it is given up to resting tissues, i.e., only 25 per cent of the available oxygen is utilized. This is sometimes called the *coefficient of utilization.*

If the tissue is active and not resting the "suction" for oxygen is greater because the tension of oxygen in the tissue fluids is reduced, possibly even to zero if the cells are using oxygen very actively. At the same time the CO_2 tension and hydrion concentration of the tissue fluids are increased. Consequently much more oxygen is taken from the blood, which may emerge on the venous side containing less than 10 ml. per 100 during moderate activity and as little as 5 ml. per 100 during very vigorous exercise. Since active tissues also produce heat the temperature of the blood is raised in passing through the capillaries of such areas and this also helps to remove oxygen from hemoglobin. The blood may give up as much as 80 per cent of its oxygen in passing through an active tissue.*

There is another very important factor in the supply of oxygen to the tissues, namely, the rate of blood flow through the capillaries and the number of capillaries through which it flows. The circulation is so adjusted in resting tissues that the cells get all the oxygen they need, but, as a rule, there is a large margin for further increase both in the rate (or volume) of total blood flow through the tissue and in the total capillary surface over which it is exposed for the diffusion of gases. When a muscle, for example, becomes active, its blood vessels dilate and capillaries previously closed become open. In this way the total amount of oxygen yielded to the tissue can be greatly increased and if—as happens in exercise—the cardiac output and arterial blood pressure also increase, the additional supply of oxygen furnished by circulatory changes may be enormous. Even without any increase in the circulation as a whole the volume of blood flowing through a given tissue is usually increased when the tissue becomes more active. In some cases, such as the salivary gland, the increase in blood flow is out of proportion to the increase in oxygen consumption, and the venous blood leaving the gland during stimulation of the chorda tympani nerve is likely to contain more oxygen than it did before stimulation. The same

*The dissociation of oxygen from oxyhemoglobin ($HbO_2 \rightarrow Hb + O_2$) is greatly influenced by temperature while the combination of oxygen with reduced hemoglobin ($Hb + O_2 \rightarrow HbO_2$) is much less affected. This is a matter of considerable importance because it helps to supply the tissues with the oxygen they need without placing the oxygenation of the blood in the lungs at the mercy of changes in the temperature of the environment. See Barcroft.[15]

thing is true of the kidney and probably of the brain; i.e., when the activity of tissues such as these is increased the local circulation is so greatly augmented that the increased call for oxygen is fully met without the necessity of abstracting even as much oxygen from each unit of blood as was the case when the tissue was at rest. In the muscles the blood is usually reduced more completely during work than during rest; this is probably because the area of the capillaries through which blood passes is increased more markedly in the muscles than in other tissues, the circulatory readjustment in the muscles thus being

TABLE XXVI

ORGAN	CONDITION OF REST	OXYGEN USED PER MINUTE PER GRAM OF ORGAN (ML.)	CONDITION OF ACTIVITY	OXYGEN USED PER MINUTE PER GRAM OF ORGAN (ML.)
Voluntary muscle	Nerves cut. Tone absent	0.003	Tone existing in rest Gentle contraction Active contraction	0.006 0.020 0.080
Unstriped muscle	Resting	0.004	Contracting	0.007
Heart	Very slow and feeble contractions	0.007	Normal contractions Very active	0.05 0.08
Submaxillary gland	Nerves cut	0.03	Chorda stimulations	0.10
Pancreas	Not secreting	0.03	Secretion after injection of secretin	0.10
Kidney	Scanty secretion	0.009	After injection of diuretic	0.113
Intestines	Not absorbing	0.02	Absorbing peptone	0.03
Liver	In fasting animal	0.01-0.02	In fed animals	0.03-0.05
Brain	Inactive (artificial respiration)	0.035	Dyspnea	0.10
Suprarenal gland	Normal	0.045	----------	----------

such as to favor more complete removal of oxygen from the blood while in most other tissues it is such as to increase the total volume of blood passing through a capillary area that changes relatively little.

It is evident that if one wishes to know the amount of oxygen used by a given tissue it is necessary to know (1) the volume of blood which flows through it, as well as (2) the oxygen content of the arterial blood, and (3) the oxygen content of the venous blood leaving the tissue; in order to compare the oxidative processes of different tissues one must also know (4) the weight of the tissue, and the results are usually reported as milliliters of oxygen consumed per gram of tissue per minute. The difficulties in such investigations are biological rather than chemical; the oxygen content of the blood samples can be determined with great accuracy, but the accurate measurement of blood flow is usually difficult and this factor looms much larger in the calculation than the amount of oxygen taken out of each unit of blood. The samples of arterial and venous blood must be collected simultaneously and the blood flow must also be measured at the same time, for otherwise the conditions under which the two samples were

collected may not correspond, and the blood flow when measured may not be that which existed when the samples were collected. These precautions are not always taken by investigators in this field, and the quantitative significance of some of the results obtained is therefore somewhat doubtful. There can be no doubt that increased activity of an organ means increased demand for oxygen. The only doubts concern quantitative data; i.e., how does the amount of oxygen used by one organ compare with the amount used by another, at rest and during activity? Table XXVI gives representative figures.

PART V

METABOLISM AND NUTRITION

By Chalmers L. Gemmill

CHAPTER XLVIII

TISSUE METABOLISM

Physiology is the science of the normal functions and phenomena of living things (Fulton[78]). Behind each function and phenomenon are chemical changes which convert potential energy into useful work. Both physiologists and biochemists have contributed to the study of these chemical changes. Physiologists are interested in the neural and hormonal control of chemical processes and in the chemical reactions involved in organ functions. By reducing the reactions to their simplest terms, biochemists obtain information concerning the possible enzymatic reactions, their substrates, the end products, and the methods of control of such reactions. Physiologists use the knowledge derived from such procedures to explain organ function and the control of such function. Both approaches are necessary for a full understanding of metabolism and the student of the subject must be able to appreciate both viewpoints. For this reason, a chapter on tissue respiration discussed from the standpoint of enzymatic reactions is included in the section on metabolism.

A study of tissue metabolism involves a consideration of the biochemical reactions which release energy for cellular processes. These reactions may be divided into two types, the *aerobic* and the *anerobic*. The magnitude of these two processes in various organs is given in Table XXVII. The aerobic reactions

Table XXVII

Metabolism of Various Tissues Measured Manometrically (Krebs,[27] and Dixon[209])

Animal	Tissue	Temp.	Solution	Q_{O_2}	$Q^{N_2}_G$	$Q^{O_2}_G$
Rat	Kidney	37.5	Ringer	−21.0	+3.7	0
Mouse	Kidney	37.5	Ringer	−20.4	–	0
Dog	Kidney	37.5	Ringer	−18.4	–	0
Rat	Liver	37.5	Ringer	−8.8 to −13.2	+3.3	+0.6
Rat	Brain	37.5	Ringer	−10.7	+19.1	+2.5
Guinea pig	Red cells	37.5	Blood	−0.61	+0.43	–
Rat	Salivary gland	37.5	Ringer	−9 to −24	+3.3 to +6.9	–
Rat	Diaphragm	38.0	Ringer	−6.0	–	–
Rat	Carcinoma	37.5	Ringer	−2.5 to −12.8	+25 to +40	+18 to +30

$$Q_{O_2} = \frac{\text{mm}^3\ O_2}{\text{per mg. (dry weight) per hour}}$$

$$Q^{N_2}_G = \frac{\text{mm}^3\ CO_2}{\text{per mg. (dry weight) per hour}}$$ in an atmosphere of N = anerobic glycolysis.

$$Q^{O_2}_G = \frac{\text{mm}^3\ CO_2}{\text{per mg. (dry weight) per hour}}$$ in an atmosphere of O = aerobic glycolysis.

Aerobic and anerobic glycolysis are expressed in terms of the amount of carbon dioxide liberated from the bicarbonate solution by the lactate formed in these processes.

are those in which molecular oxygen is used to complete the reaction; and the anerobic are those through which energy is liberated without the interaction of molecular oxygen. For example, the formation of lactate from glycogen is considered an anerobic process because it is completed without the interaction of molecular oxygen, but the oxidation of lactate to carbon dioxide and water is regarded as an aerobic process because it requires molecular oxygen for the completion of this reaction. The aerobic types of reactions will be considered first. A discussion of the anerobic types is reserved for the chapter on muscle, since in this tissue, glycolysis, an anerobic process, plays an important role in the liberation of energy.

Respiratory Enzymes

Definition of Oxidation.—Aerobic respiration deals with the oxidation of metabolites in which molecular oxygen is used to complete the reaction and in which carbon dioxide and water are liberated. The term *oxidation* implied originally a taking up of molecular oxygen by a molecule; and the converse process, *reduction,* involved a removal of oxygen from a molecule. Later, it was recognized that the removal of hydrogen from a molecule is also oxidation and that the addition of hydrogen is a reduction. Finally, it was demonstrated that a transfer of electrons without an equivalent transfer of hydrogen or oxygen is also an oxidation. These three processes may be illustrated by the following oxidations and reductions of the ferrous-ferric ion system (Clark[5]).

$$2\ Fe^{++} + \tfrac{1}{2}\ O_2 = 2\ Fe^{+++} + O^{--} \quad (1)$$

$$2\ Fe^{++} + 2\ H^{+} = 2\ Fe^{+++} + H_2 \quad (2)$$

$$Fe^{++} = Fe^{+++} + e \quad (3)$$

Fundamentally, the first and second equations are equivalent to the third, for, in the first reaction, oxygen gains electrons from iron, producing iron with a more positive valence and oxygen with a more negative one; in the second reaction, the ferrous ion loses an electron to the hydrogen ion, thereby becoming a ferric ion and the hydrogen gains an electron, becoming molecular hydrogen. Therefore, oxidation may be defined as a change of an atom or ion from a state of lower to higher valence whereas reduction is a change to a lower valence. Since the substance reduced becomes more negatively charged than the original, it acts as a base for attracting hydrogen ions. The taking up of hydrogen, therefore, may be a secondary reaction to the electron shift. Hydrogen may be transferred primarily, or an electron may be transferred followed by secondary hydrogen transfer. However, which of these two processes occurs depends on the dissociation constant of the reduced substance and on the hydrogen ion concentration of the medium. The terms *hydrogen acceptor, electron acceptor, hydrogen donator,* and *electron donator* may be applied to the respective atoms or ions involved. It is obvious from the examples given, that every oxidation involves a simultaneous reduction.

Cyclic Processes.—Many organic substances have the ability to combine with molecular oxygen. Some of these oxidations may proceed with explosive violence. This fact has given rise to the idea that these reactions represent a direct interaction of oxygen with the organic material. Closer study has revealed that these reactions are, for the most part, indirect and cyclic processes. In the biological field, indirect and *cyclic* processes are also employed for oxidation. The majority of the organic molecules used for food materials are oxidized very

slowly outside the body. In contrast, when inside the body these molecules or parts of the molecules are destroyed very rapidly through accelerating mechanisms which involve enzymes, coenzymes, and carriers—reactions which are cyclic and indirect processes. These findings, although for the most part made on isolated enzymatic systems, are being applied to normal tissue metabolism, vitamin deficiencies, and hormone activity, and will, in the future, be used to explain many other normal and pathological metabolic changes. Therefore, a thorough understanding of the fundamental principles of biological oxidations is essential for the appreciation of the modern trends in metabolic study and of the future advances in this field.

Enzymatic Activation.—Two general ideas have dominated the development of biological oxidations. The one, sponsored chiefly by Warburg, is that molecular oxygen must be activated by an enzymatic process before the organic molecule may be oxidized. The other, developed from the work of Wieland and Thunberg, is that the hydrogen atoms in the organic molecule must be activated by a catalyst before being removed by molecular oxygen or any other suitable hydrogen acceptor. The enzymes involved in the activation of oxygen are called *oxidases* and those for the activation of hydrogen are termed *dehydrogenases.* It was discovered that the majority of enzyme systems involving hydrogen transfer do not enable the activated hydrogen to be transferred to molecular oxygen unless the oxygen is also activated by its specific catalyst. This finding led to a coordination of the two schools of thought and resulted in the theory that the hydrogen and oxygen are activated and are united through a chain of specific carriers.

The terms *dehydrogenase, oxidase, activation,* and *carrier* need further explanation. By definition, an *enzyme* is a biological catalyst that accelerates a reaction to its equilibrium point. A *dehydrogenase,* in the true sense of the word, accelerates a transfer of hydrogen from the metabolite to an acceptor as in reaction 4.

$$AH_2 + B \rightleftharpoons A + BH_2 \qquad (4)$$

However, it may also accelerate the reversal of this reaction if substances A and BH_2 are added to the enzymatic solution. Here, the hydrogen is transferred from the so-called acceptor and given to the so-called donator. Since, in this case, a dehydrogenase brings about an increase in the velocity of a reaction until the equilibrium point is reached, the original meaning of the term, *dehydrogenase* (i.e., an enzyme which removes hydrogen), has lost its significance. This term is still used, however, to describe an enzyme which accelerates the transfer of hydrogen, generally from the metabolite to the acceptor. As explained in the first section, this transfer may be one of hydrogen or one in which an electron is transferred with or without a secondary transfer of hydrogen. The end result is the same, the metabolite is oxidized and the hydrogen or electron acceptor is reduced. There are many dehydrogenases; in fact, it has been claimed that each organic substance metabolized by the tissues has its specific dehydrogenase.

Many theories have been presented to explain the actual mechanism of enzymatic activation of hydrogen in an organic molecule and of molecular oxygen. None of these theories is satisfactory. Therefore, *activation* may best be defined in terms of the result: it enables an organic molecule, otherwise stable, to give up hydrogen at a finite velocity when acted on by a dehydrogenase, and it enables molecular oxygen to react more rapidly with hydrogen in the presence of an oxidase.

Cytochrome Oxidase.—Oxygen has a specific enzyme for its activation. Knowledge of this enzyme has come from three entirely separate sources: the study of the formation of indophenol by the indophenol oxidase, the study of the respiratory ferment by Warburg, and of cytochrome oxidase by Keilin. It is now known that the enzyme is the same in the three systems.

Indophenol oxidase, an enzyme which accelerates the conversion of α-naphthol and dimethyl-p-phenylenediamine (Nadi reagent) to indophenol, has been known for a long time. This enzyme is present in a majority of animal tissues, in bacteria, and in yeast. Because only nonbiological reagents were used in the test for the presence of this enzyme, little importance was attached to the results except that the presence of a powerful oxidase in tissues was noted. The similarity of this enzymatic activity to that of cytochrome oxidase will be discussed later.

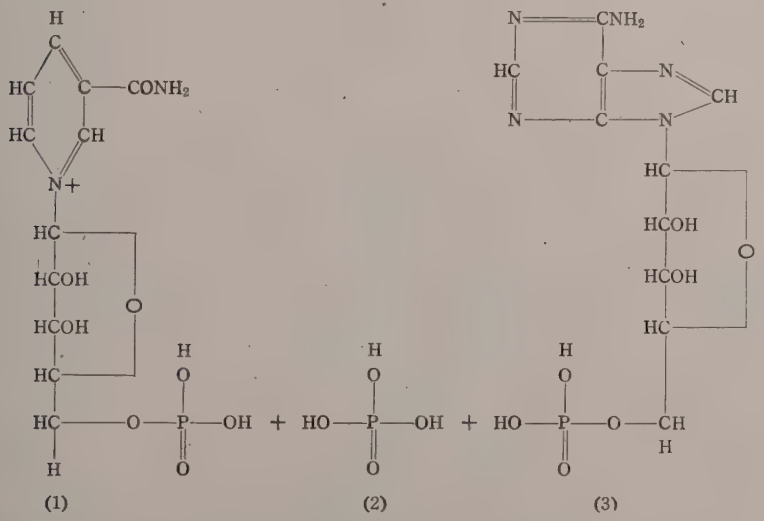
The second independent line of attack came from the work of Warburg. Warburg postulated that the oxygen-transferring enzyme of respiration contained iron because of the ability of cyanide and carbon monoxide to inhibit respiration. It is well known that heavy metal ions react with cyanide to form compounds which do not dissociate easily. In the case of a heavy metal catalyst this combination would block the active group and prevent the reduction of the heavy metal. Not all heavy metal catalysts are, however, inhibited by cyanide, for the inhibition depends on the nature of the metal and on the type of linkage to other parts of the molecule. But, since cell respiration is nearly 100 per cent inhibited by suitable cyanide concentrations, Warburg stated that the respiratory enzyme was an iron-containing component of a heme type. The evidence that it was of a heme type came from an indirect determination of the absorption spectrum of this compound. Having discovered that carbon monoxide inhibits the oxygen uptake of yeast, and knowing that the reaction of carbon monoxide with hemoglobin is reversed by the action of light, Warburg[38] radiated yeast with light of various wave lengths and measured the respiratory activity at these wave lengths. He discovered that light dissociated the combination of carbon monoxide and the respiratory ferment. This dissociation increased respiration. In this reaction it was evident also that different wave lengths had different efficiencies. From this study of the relative effects of various wave lengths, Warburg calculated the absorption spectrum of the respiratory ferment and found that it closely resembled that of known carbon monoxide derivatives of hematin.

The connection of indophenol oxidase and the respiratory ferment with the cytochrome system resulted from the work of Keilin. Keilin[23-26] studied the indophenol oxidase system in yeast and found that the properties of this enzyme were very similar to those found by Warburg for his respiratory ferment. The indophenol oxidase activity was inhibited by cyanide or carbon monoxide and the inhibition caused by carbon monoxide was reversed by light. In fact, all the various reagents used to study the respiratory ferment reacted in the same manner with the indophenol oxidase. Since molecular oxygen cannot combine directly with cytochrome, and since both the respiratory ferment and indophenol oxidase may reduce oxidized cytochrome, Keilin postulated that these enzymes were the same. The specific property of this enzyme is to activate oxygen in order that it may be used in the reduction of cytochrome—a true cytochrome oxidase function. Later work (Stotz, Sidwell and Hogness[34]) has shown that the indophenol oxidase metabolizes its nonbiological substrate through cooperation with cytochrome.

Respiratory Coenzymes

Several important coenzymes of the respiratory mechanisms have been isolated and their constitution determined. A coenzyme may be defined as a substance produced by living cells, necessary for enzymatic reactions, of lower molecular weight than the protein portion of the enzyme, heat stable and dialyzable (Baumann and Stare[3]). The distinction between coenzyme and enzyme varies in different cases. In some, the active group, which is called the coenzyme, is combined with a protein that is inactive by itself; in other cases, the coenzyme is combined with a protein which has true enzymatic activity by itself. In this latter case, the coenzyme further accelerates the natural activity of the proteins. The respiratory coenzymes are compounds which may be reversibly oxidized and reduced. By this property they act as hydrogen or electron acceptors or donators.

Pyridine Nucleotides.—It has been known for a long time (Harden and Young[21]) that the fermentation of cell-free extracts of yeast was accelerated by the addition of a thermostable fraction of yeast juice. This portion was termed "coenzyme" as it accompanied the enzyme from yeast. The general distribution and importance of this coenzyme were demonstrated by Meyerhof,[31] who showed that the same activity could be obtained from a substance present in muscle and in milk. This substance not only aided fermentation but also accelerated the oxygen uptake of muscle. Through the work of Warburg and his associates,[40, 41] the chemical nature and the specific biological importance of this substance has been disclosed. It is a diphosphopyridine nucleotide consisting of adenine, nicotinic acid amide, two molecules of phosphoric acid and two of pentose:



(1) + (3) = Diphosphopyridine nucleotide + H_2O

(1) + (2) + (3) = Triphosphopyridine nucleotide + $2H_2O$

Various names have been given to this substance: coenzyme I, yeast coenzyme, codehydrase I, and others. Since the constitution has been determined, it would be best to call it by its chemical name, diphosphopyridine nucleotide or DPN. Warburg isolated another coenzyme in his studies of the oxidation of hexosemonophosphate by red blood cells. This coenzyme is similar to DPN with the exception that it contains three molecules of phosphoric acid. This molecule has been called coenzyme II, but since the chemical constitution is known, it will be called triphosphopyridine nucleotide or TPN.

The remarkable discovery which came out of this work was the high degree of specificity of DPN and TPN in their coenzymatic activity, since most of the enzymes require either DPN or TPN and only a few may use both interchangeably. Why one molecule of phosphoric acid in the coenzyme should make such a difference has not been explained. The substrates which are known to be oxidized by means of the pyridine nucleotides are given in Table XXVIII.

TABLE XXVIII

SUBSTRATES OXIDIZED BY MEANS OF PYRIDINE NUCLEOTIDES (BALL[1])

SUBSTRATE	ENZYME SOURCE	COENZYME	
		DPN	TPN
Hexosemonophosphate	Red blood cells	–	+
	Yeast	–	+
Triosephosphate	Muscle	+	–
	Yeast	+	–
Alcohol	Yeast	+	–
Lactate	Muscle	+	–
Glycerolphosphate	Muscle	+	–
Glutamic acid	Liver	+	+
	Yeast	–	+
	B. coli	–	+
	Plants	+	–
Glucose	Liver	+	+
β-hydroxybutyrate	Muscle	+	–
Malate	Muscle	+	–

It may be noticed from the table that the enzyme for the oxidation of glutamic acid uses both DPN and TPN but only when the enzyme source is from the liver. Glucose dehydrogenase also uses both coenzymes.

Riboflavin Phosphoric Acid.—In his study of hexosemonophosphate oxidation, Warburg[39] discovered a coenzyme which aided in the oxygen uptake of that system. This coenzyme was shown to be a phosphorylated riboflavin which needed for its activity a protein molecule. The complete molecule is called a flavoprotein or yellow enzyme. More recent work has shown that this coenzyme is a flavin adenine nucleotide with the following components.

Phosphate—ribose—adenine
|
Phosphate—ribose—flavin

The similarity of this molecule to DPN may be seen by writing formula (1) of DPN in the same manner.

Phosphate—ribose—adenine
|
Phosphate—ribose—nicotinic amide

In addition to this flavoprotein, numerous others have been described. The chemical and biological properties of the more important of these compounds have been summarized in Table XXIX.

TABLE XXIX

PROPERTIES OF FLAVOPROTEINS (DIXON[7])

	YELLOW ENZYME OF WARBURG	LACTOFLAVIN	COENZYME FACTOR	COENZYME OF D-AMINO ACID OXIDASE
Source	Yeast	Milk	Heart	Kidney
Color	Yellow	Orange-red	Yellow	
Absorption bands at	380:465	350:450	359:451	
Molecular weight	78,000	280,000		
Reacts with methylene blue	+	+	+	+
Oxygen	+	+(?)	−	+
Cytochrome C	+	+	−	
Red. DPN	+	+	+	−
Red. TPN	+	+(?)	−+*	−

*Two forms present (von Euler[37]; Green[16]).

Flavoprotein was shown by Warburg to be the essential link between the TPN and oxygen in the oxidation of hexosemonophosphate.

Hexosemonophosphate + enzyme + TPN + flavoprotein + O_2.*

Since this system is not inhibited by cyanide, it was thought that such a mechanism might explain the residual oxygen uptake in some cells following poisoning with cyanide. Recent work, however, has given a more important position to the flavoproteins. Green and his associates[16] and von Euler[37] have described a "coenzyme factor" or "diaphorase" which had the property of oxidizing the reduced DPN and of being reoxidized by molecular oxygen or cytochrome. Straub[35] isolated from heart muscle a new flavoprotein which Green and Corran and Straub[20] had shown to be identical with this coenzyme factor. Diaphorases I and II which act with DPN and TPN, respectively, have been described (Alder, von Euler and Günther[12]). Since the DPN or TPN do not have the ability to reduce cytochrome or to take up molecular oxygen, this coenzymal link is necessary between the DPN or the TPN systems and cytochrome. These findings place flavoproteins in the direct line of oxidations and these substances may be considered as dehydrogenases of DPN or TPN.

Cytochrome.—Although not considered as a coenzyme, cytochrome is a natural carrier and will be discussed in this section. MacMunn[29, 30] described a pigment in muscle which, when reduced, had characteristic absorption bands and which, when oxidized, had none. He extracted this pigment from muscle and gave to the substance the name "modified myohematin." This pigment was forgotten until Keilin discovered the wide distribution of this substance in tissues that use oxygen and described its important role in oxidative processes. Keilin gave to this substance the name *cytochrome*. Cytochrome has been subdivided into three components, *a*, *b*, and *c*, by their characteristic absorption spectra.

Cytochrome *c* is soluble and may be readily extracted from cells. It has been purified and partially identified (Theorell[36]). The biological importance of

*In this and the following section the components of the enzyme systems will be listed with + signs. This does not denote a stoicheiometric reaction between components; it merely shows the components that must be present in order to obtain a reaction.

the cytochromes is that they may be rapidly oxidized and reduced, and when they are present with special enzyme systems, they aid in the acceleration of oxygen uptake. It has been calculated that practically all of the respiratory activity of yeast is connected with the cytochrome system. Other examples of cytochrome activity will be given in the following sections.

CLASSIFICATION OF RESPIRATORY ENZYME ACTIVITIES

Respiratory enzymatic activity may be classified by the number of components necessary for oxidation of the substrate.

Aerobic Dehydrogenase Activity.—The aerobic dehydrogenase chain possesses the smallest number of components. The enzymes activate hydrogen of the substrate, but the chain requires neither cytochrome nor cytochrome oxidase, and can reduce dyes or oxygen directly. The outstanding enzymes of this group are xanthine oxidase, which has the property of oxidizing xanthine or aldehydes, and d-amino acid oxidase, which acts on the d- form of amino acids—the "unnatural" amino acids. Warburg and Christian[42] have shown that d-amino acid oxidase is a flavoprotein, and Ball[14] has demonstrated a comparable substance associated with xanthine oxidase. These two enzymes, therefore, carry out their reactions through the following components:

$$\text{Substrate} + \text{flavoprotein} + O_2$$

Uricase also belongs in this group but it is unique, for it uses oxygen as a specific receptor and does not need a flavine adenine nucleotide for its activity:

$$\text{Uric acid} + \text{uricase} + O_2$$

This particular reaction has been studied extensively by Keilin and Hartree.[24]

Anaerobic Dehydrogenase Activity.— The anaerobic dehydrogenase chain forms the next group. It is termed anaerobic because it needs intermediate substances to complete the oxidation of substrates. The enzymes activate hydrogen so that it either reduces cytochrome directly or reduces DPN or TPN which in turn reduces a flavoprotein and then finally cytochrome. It was originally thought that a few dehydrogenase systems in this class had the property of producing reduction of cytochrome directly by means of activated hydrogen. These enzymes in this system were believed to be lactate dehydrogenase from yeast, the α-glycerophosphate dehydrogenase in muscle, and the succinate dehydrogenase. Recent experimentation indicates, however, that some of these dehydrogenase systems may require another intermediate substance between the substrate and cytochrome. Hopkins[22] and Stern,[33] in work with the succinate dehydrogenase have described an additional activating factor necessary for the complete reaction, and it is possible that another such additional factor may be needed for lactate dehydrogenase activity.[17] Further investigation of this question is necessary, however, before these factors can be definitely added to the scheme. At the present time the following components are considered to enter into this type of reaction:

$$\text{Substrate} + \text{dehydrogenase} + \text{cytochrome} + \text{cytochrome oxidase} + O_2$$

All of the other types of anaerobic dehydrogenases require the complete system:

$$\text{Substrate} + \text{dehydrogenase} + \text{DPN (or TPN)} + \text{flavoprotein} + \text{cytochrome} + \text{cytochrome oxidase} + O_2$$

Each carrier may react with its immediate neighbor. The flavoprotein used by Warburg in his red blood cell system combined directly with oxygen. However, Theorell observed that the velocity of the uptake of oxygen was greater if the cytochrome system was also present. Therefore, the more normal system uses the complete chain. All of the substrates listed in Table XXVIII are oxidized by the complete system.

Many other carriers may be placed in these systems. For example, Szent-Györgyi[10] claims that the succinate-fumarate system and the malate-oxaloacetate systems act as hydrogen transporters with a flavoprotein joining the two systems. The ability of one system to oxidize or reduce another depends on the oxidation-reduction potential of the two systems and the carrier. (Green et al.[15, 18, 19].) Whether all of these systems play a rôle in the oxidation of substrates in the intact cell is not known; however, the component parts are present and may be isolated experimentally.

The final result of the oxidations described above is the production of CO_2 and of water. The hydrogen in the water may be the original hydrogen of the substrate if hydrogen transport takes place along the whole chain; or, if electron transport takes place, the electrons will act on the oxygen in such a manner that it will combine with any hydrogen ion present in the solution. If hydrogen peroxide is formed, it will be acted upon by either a *peroxidase* or a *catalase,* either of which will convert the peroxide into water and oxygen. The peroxidase has the property of activating the oxygen as it is formed in order that it may again be used in biological oxidations.

Decarboxylation.—The carbon dioxide formed in biological oxidations comes from a process of decarboxylation. This process also needs a coenzyme. Neuberg[32] demonstrated that an enzyme, carboxylase from yeast, had the property of converting pyruvic acid into acetaldehyde by a process of decarboxylation. Auhagen[13] showed that this enzyme needed a coenzyme (cocarboxylase) which Lohmann and Schuster[28] later isolated. The latter observers showed that the coenzyme is phosphorylated vitamin B_1.

Most of the carbon dioxide formed in biological oxidations is supposed to come from decarboxylation. This means that food material must pass through an organic acid stage before being finally burnt. It also means that the carbon dioxide given off by the body comes from the carbon and oxygen in the food material. The other end product, water, contains the molecular oxygen that we breathe and the hydrogen that was originally present in organic food material. This hydrogen may have come not from a given molecule which became oxidized but from the store of hydrogen ions in the body. The difficulty of following oxygen, carbon, or hydrogen through the maze of metabolic events is obvious. Tagged atoms will be of great aid in the final elucidation of these processes.

CHAPTER XLIX

ENERGY METABOLISM

Metabolism, a term derived from a Greek word meaning change, may be defined as "the sum of all the physical and chemical processes by which living organized substance is produced and maintained, and also the transformation by which energy is made available for the uses of the organism". (Dorland[11]). The formation of molecules of higher from those of lower energy content and their incorporation into organized tissue constitute the process of *anabolism.* This has not been studied as extensively as has the process of *catabolism,* the breakdown of large unstable molecules with the release of energy. The reason that catabolism has received the greater attention is that one of the essential features of the breakdown is an oxidative process, the magnitude of which may be measured easily by determining the total energy evolved or the quantity of oxygen used. On the other hand, it is very difficult to follow the chemical and energy changes associated with anabolism.

METHODS

Two general methods are available for the study of metabolism in animals. In the first, the constituents of the ingested food are compared with those of the excretory products. From this a balance may be constructed showing the amounts of material left in the body and the types of end products produced. This method of experimentation deals with what has been termed *general metabolism.* In constructing a balance sheet of general metabolism, substances must be selected which are common to intake and output. For the most part the intake comprises water, oxygen, proteins, fats, carbohydrates, and minerals. The output consists chiefly of carbon dioxide, water, minerals, and various nitrogenous constituents of the urine. The dissimilarity in chemical structure between the substances taken in and most of those excreted limits us, in balancing the one against the other, to a comparison of the elements into which each can be broken by chemical agencies. From balance sheets of intake and output of carbon and nitrogen and from information obtained by determining the ratio between the amounts of carbon dioxide excreted and oxygen consumed (the respiratory quotient), it is possible to draw some conclusions regarding the relative amounts of protein, fat, and carbohydrate that have been involved in the metabolic processes.

The second method used in the study of metabolism deals with the chemical changes which individual foodstuffs undergo between ingestion and excretion. In this, instead of contenting ourselves with a comparison of the raw material taken in and the finished product of the animal factory, we seek to learn something of the particular changes undergone by each kind of material as it yields energy for cellular processes or enters into the repair of worn-out tissues. Such is the method of studying the subject of *special metabolism.* In this case balance sheets tell practically nothing of the changes under investigation. For example, suppose that when a substance, A, is fed, an amount of

another substance, B, is found in the urine. This fact may be interpreted in any one of several ways; it may mean that B is one of the intermediate products of the breakdown of A; if only a small amount of B appears, it may signify that there are two or more ways of metabolizing A, B representing the end product of only one of these chemical pathways; finally, it may be interpreted to mean that B is derived from an intermediate product by a side reaction and is not formed in the direct line of changes. Obviously experiments directed toward a study of general metabolism may give little or no information concerning special metabolism.

Special Methods

Various special methods have been employed in investigating problems in special metabolism. The more important of these are described below.

Feeding Experiments.—In the prosecution of experimental work directed toward the determination of the intermediate products of the metabolism of some substance a method of exclusion may be used. The chemically possible intermediates are fed to an animal and the excreta studied to determine which of these are oxidized in the body and which pass through unchanged. For example, let us suppose that oxalic and acetic acids are the chemically possible intermediates in the breakdown of some ingested substance. They are fed and it is found that oxalic acid appears in the excreta while acetic acid does not; the latter has apparently been oxidized. Therefore, acetic acid may be an intermediate product. This method, however, gives only circumstantial evidence.

Another method used extensively in this type of work involves the introduction of a ring in the molecule of the substance under investigation. It is then fed with the expectation that the ring may block part of the oxidative processes to which the substance is normally exposed and thus allow intermediate compounds to appear in the urine. One serious objection to this method is that introduction of the ring may so change the molecule that its metabolism does not proceed along the usual pathway.

Perfusion.—Perfusion of organs has been used in studying special metabolism. Valuable information has been obtained by adding substances to the perfusing fluid and detecting the intermediate products in the perfusate. Older techniques proved inadequate because the perfused organ soon became edematous, but modern methods permit perfusion for fairly long periods of time and enable the experimenter to follow the intermediate metabolism with fair accuracy. Sometimes analysis of samples of blood from the artery and vein of an organ in situ will give valuable information concerning metabolic changes taking place in that organ.

Tissue Slices.—During the past ten years the tissue slice method has become very popular among investigators in this field of physiology. Thin slices of tissue are shaken in a medium containing the substance to be metabolized. Subsequently the possible intermediates are determined by microchemical analysis of the medium and tissue. This method has the advantage over that of perfusion in that many experiments may be performed and the results treated statistically. It possesses the disadvantage that when the tissue has become abnormal no obvious signs of this make their appearance. Also, the amounts of material formed by the metabolic changes in thin slices of tissue are so small that they are difficult to determine with great accuracy.

Isotopes.—For many years, the physiologist has accepted the physicist's concept of the atom in dealing with solutions, for example, that of the hydrogen ion. More recently the newer ideas of the physicist have come into use in metabolic studies. Especially is this true of the labeled molecules (i.e., molecules made radioactive or those containing natural isotopes); hence it becomes necessary to discuss their production and use.

The new concepts of the physicist are based on the following discoveries (Du Bridge[55]):

1. The discovery, measurement, and separation of isotopes of the chemical elements (Aston, Bainbridge, Urey).

2. The development of machines for accelerating charged particles to very high energies, i.e., the cyclotron (Lawrence) and the electrostatic generator (Van de Graaff).

3. The transmutation of elements.
   a. By natural alpha-particles (Rutherford, 1919).
   b. By artificially accelerated protons (Cockcroft and Walton, 1932).

c. By deuterons (Lawrence, 1933).
d. By neutrons (Feather, 1932).

4. The discovery of the positron (Anderson, 1932).
5. The discovery of the neutron (Chadwick, 1932).
6. The discovery of induced radioactivity (Curie-Joliot, 1934).

Structure of Atoms.—A working knowledge of the structure of the atom is necessary for an understanding of the application of nuclear physics to metabolic study. The *atom* consists of two portions, the nucleus and the surrounding electrons. The nucleus is composed of *neutrons* of mass 1, carrying no charge, and the *protons* of mass 1, carrying a positive charge. The sum of the neutrons and protons determines the mass or atomic weight of the atom. The positive charges on the protons in the nucleus are balanced by electrons, units with mass of 0.00055 and carrying a negative charge. The electrons are arranged in planetary systems around the nucleus. The complete designation of an atom may be given as X_z^w where z is the atomic number (i.e., the number of protons in the nucleus or the number of electrons in the planetary system), X is the symbol of the element and w is the closest whole number to the atomic weight. The symbol for an electron is e_{-1}^{0}, which means that its mass approximates 0 and it carries a charge of –1. The electrons in the planetary orbits are easily removed. In contrast, it requires tremendous energy to remove a neutron from the nucleus of an atom.

An isotope of an atom is an element that has the same number of electrons in the planetary space but has more or fewer neutrons in the nucleus than the original atom. Since the number of electrons determine the chemical characteristics of the atom, this factor would not change. The mass changes because of the addition or subtraction of unit masses, the neutrons, from the nucleus. Isotopes are divided into two types, *stable* and unstable or *radioactive.*

TABLE XXX

ATOMIC NUMBERS, ATOMIC WEIGHTS AND STABLE ISOTOPES OF SOME ELEMENTS OF BIOLOGICAL INTEREST (ROBERTSON[63])

ELEMENT	SYMBOL	ATOMIC NUMBER	ATOMIC WEIGHT	MASS NUMBER OF ISOTOPES
Hydrogen	H^1	1	1.0081	1,2,3
Heavy Hydrogen (Deuterium)	H^2 or D	1	2.0147	2,0
Lithium	Li	3	6.94	6,7
Carbon	C	6	12.00	12,13
Nitrogen	N	7	14.01	14,15
Oxygen	O	8	16.00	16,17,18
Sodium	Na	11	23.00	23
Magnesium	Mg	12	24.32	24,25,26
Phosphorus	P	15	31.02	31,0
Sulfur	S	16	32.06	32,33,34
Chlorine	Cl	17	35.46	35,37
Potassium	K	19	39.10	39,40,41
Calcium	Ca	20	40.08	40,42,43,44
Iron	Fe	26	55.84	54,56,57
Lead	Pb	82	207.22	204,206,207,208

The isotopes are used in metabolic study for labelling certain atoms in order that their metabolic history may be traced through the body. In order to be suitable for a tag, an isotope must not be present in the body in any large concentration, must be easy to determine, and if unstable, must have a life of suitable period for biological research. The stable isotopes used in metabolic research are H_1^2, O_6^{18}, N_7^{15}, and C_6^{13}. (Table XXX.) Many radioactive isotopes have been prepared, P_{15}^{32} being one that has been used extensively for the study of phosphate transfer in the body. The radioactive isotopes may be divided into two classes, those naturally occurring and those artificially prepared. The naturally occurring isotopes, such as radioactive lead, have been used as tracers. Since only a few such atoms are known, the production of artificial radioactive isotopes has enlarged this field.

There are several methods of preparing isotopes. The stable isotopes may be obtained by fractionation of the naturally occurring elements. Heavy hydrogen, H_2^1, consisting of one neutron and one proton in the nucleus and one electron in the planetary system, occurs in water, and heavy nitrogen, N_7^{15}, with 8 neutrons and 7 protons in the nucleus and 7 electrons in the planetary system is present in atmospheric air.

Radioactive isotopes are prepared by the ejection of neutrons from the nucleus. This may be done by the action of protons, deuterons, alpha-particles or gamma-rays. Alpha-particles are liberated during the decomposition of radium and consist of a helium nucleus. Thus they are composed of two neutrons and two protons and carry a positive charge of 2, the symbol being He_2^4. The γ rays liberated in the decomposition of radium are true radiations of strong penetrating power. The classical example of the method for separation of neutrons is that of the action of alpha-particles on beryllium.

$$Be_4^9 + He_2^4 = C_6^{12} + n_0^1$$

Another example is the bombardment of beryllium with deuterons, the ions of heavy hydrogen.

$$Be_4^9 + H_1^2 = B_5^{10} + n_0^1$$

In the first equation beryllium is converted into carbon by the action of alpha particles, and in the second it is converted into boron by the action of deuterons. In both cases neutrons are liberated from the nucleus. It is to be noticed that the sum of the atom numbers as well as that of the atomic masses balances on both sides of the equation. The total charge on each side of the equation must be equal.

The number of transmutations are infinite. If an unstable isotope is formed, it is converted into a stable form by the ejection of a positron or an electron. A *positron* is a particle of similar mass to an electron but carrying a positive charge. A proton in the nucleus is considered to be formed from a neutron and a positron, and a neutron is created by the combination of a proton and an electron. Thus positrons and electrons may be split from protons and neutrons with the resulting production of neutrons and protons. The symbol for the positron is e_1^0, meaning that it has a mass almost of 0 and a charge of 1.

$$\text{Proton } (H_1^1) = \text{neutron } (n_0^1) + \text{positron } (e_1^0)$$

$$\text{Neutron } (n_0^1) = \text{proton } (H_1^1) + \text{electron } (e_{-1}^0)$$

An example of such a conversion is the change of C_6^{12} to N_7^{13}. N_7^{13} is an unstable isotope and is converted into the stable C_6^{13}:

$$C_6^{12} + H_1^1 = N_7^{13}$$

$$N_7^{13} = C_6^{13} + e_1^0$$

In the first reaction, the carbon atom has gained a proton, making six neutrons and seven protons in the nucleus and seven electrons in the planetary space. This gives the atom the characteristics of nitrogen with an atomic weight of 13. One of the protons loses a positron, becoming a neutron. The atom now has seven neutrons and six protons in the nucleus, and six electrons in the planetary space. This gives the atom the characteristics of carbon with an atomic weight of 13.

Radioactive phosphorus is prepared by the action of a neutron on sulfur:

$$S_{16}^{32} + n_0^1 = P_{15}^{32} + H_1^1$$

In this reaction the neutron replaces a proton in the sulfur atom. The resulting atom has 17 neutrons, 15 protons and 15 electrons, giving it the characteristics of phosphorus with an atomic weight of 32. It has a half life of 14.8 days, ample time for most metabolic studies. Other examples will be given under their appropriate subjects.

The radioactivity of the unstable isotopes does not affect biological function, as the radioactive atom emits radiation only at the end of its career, when it changes into another element. Thus, very few of the tracer elements emit radiations during the course of a biological experiment. The small change in atomic weight of the isotopes does not affect the ability of the ion to diffuse through membranes or to take part in metabolic interchange. A serious objection is that the isotope may not be firmly bound to the compound under study and thus be lost or chemically transferred during the time of study. It has been shown, however, that heavy hydrogen bound to carbon as in a methyl group cannot be removed by exchange with water or even by treatment with hot acid or alkali. Therefore, if deuterium is removed by a reaction in the body, this interchange represents a biological change in the position of the atom. A similar stability has not been demonstrated for all isotopes and any reaction involving these substances must be accepted with the reservation that the isotope is assumed to be firmly bound in the molecule and can only be removed during the course of a true biological reaction.

THE ENERGY BALANCE

One of the forms of metabolic investigation which has yielded very important information is the study of the body's input and output of *energy*. The basis of such work is the application to biological systems of the first law of thermodynamics.

The First Law of Thermodynamics.—Count Rumford, at the end of the eighteenth century, noticed that the mechanical energy expended during the boring of a cannon was roughly proportional to the amount of heat evolved in the process. During the fifth decade of the last century Mayer, Joule and Helmholtz independently stated that a definite amount of mechanical energy produces a definite amount of heat. Their observations and discussions led to the general conclusion that energy is neither gained nor lost when it is converted from one form to another. This "law of the conservation of energy" has been applied to all forms of energy: kinetic, thermal, electric, and chemical. According to it any system in a given condition contains a definite quantity of energy and, when the system undergoes change, any gain or loss of its internal energy is equal to the loss or gain in the energy of surrounding systems (Lewis and Randall[59]). The application of this law to biological systems was one of the outstanding events in the development of our knowledge of metabolism. It involved a comparison of the actual energy expended by an animal with the energy supplied to the animal either from ingested foodstuffs or from the reserve stores of material in the body. This comparison is called the energy balance of metabolism.

The unit of energy used in work with biological systems is the large Calorie, indicated by capital C, which is the amount of heat required to raise the temperature of one kilogram of water through one degree Centigrade of temperature. The value of the Calorie varies with the level at which the temperature change of the water occurs; generally the change taken is that between 15° C. and 16° C. The caloric value of the energy supplied in the food is determined by burning a measured quantity of material in a bomb calorimeter. This apparatus is placed in a known amount of water at a certain temperature. After combustion of the material inside the bomb the resulting rise in the temperature of the water is multiplied by the volume of the water in liters to ob-

tain the caloric value. Another method (Benedict and Fox[71]) consists in measuring the oxygen used in burning the food material and then converting this value into Calories. This is an *indirect method* of determining the energy content of foodstuffs and stands in contrast with the *direct method* of the calorimeter. The caloric values obtained for commonly ingested materials are given in Table XXXI.

TABLE XXXI

GASEOUS EXCHANGE, RESPIRATORY QUOTIENT, HEAT PRODUCTION AND CALORIC VALUE OF CARBON DIOXIDE AND OF OXYGEN OF VARIOUS COMMONLY METABOLIZED COMPOUNDS (CARPENTER[50])

MATERIAL	O_2 REQUIRED TO OXIDIZE 1 GRAM ml.	PRODUCED IN OXIDATION OF 1 GRAM		R. Q.	HEAT PER LITER OF	
		CO_2 ml.	HEAT CAL.		O_2 CAL.	CO_2 CAL.
Starch	829.3	829.3	4.20	1.00	5.06	5.06
Cane sugar	785.5	785.5	3.96	1.00	5.04	5.04
Dextrose	746.2	746.2	3.74	1.00	5.01	5.01
Lactic acid	745.9	745.9	3.62	1.00	4.85	4.85
Animal fat	2013.2	1431.1	9.50	0.71	4.72	6.64
Protein	956.9	773.8	4.40	0.81	4.60	5.69
Acetone	1542.9	1157.2	7.43	0.75	4.82	6.42
Ethyl alcohol	1459.5	972.9	7.08	0.67	4.85	7.28

The values given above, especially those for the more complex substances, are still in process of standardization. The values which have been obtained for such materials as glycogen and starch, difficult to obtain in a state of chemical purity, have not been in precise agreement. Although the differences are small they become significant when used in attempts to balance the energy exchange of tissues.

Essentially the same methods are used to measure the energy liberated by the animal body. Here again it may be determined *directly,* by placing the animal in a calorimeter, or *indirectly,* by measuring the amount of oxygen used or the amount of carbon dioxide given off and then converting these values into Calories. From the respiratory quotient the ratio of the volume of carbon dioxide given off to the volume of oxygen taken in during the same interval of time, a rough indication of the type of food material metabolized is obtained. It will be advantageous to give an outline of the techniques of the two methods.

METHODS

The Direct Method

The direct method has the advantage that it measures in Calories the output of energy. When small animals are studied the simplest form of apparatus is a Dewar flask in which the animal is placed and the resulting temperature change recorded by a sensitive thermometer. Meyerhof[85] used this method to determine the heat produced during the formation of lactic acid in frogs' muscles. Hill[82] constructed a differential calorimeter by making use of two flasks in each of which was placed one junction of a thermocouple. In using such an apparatus the animal or tissue is placed in one flask and the other acts as a control whereby the effects of changes in external temperature upon the recording mechanism are excluded. This type of apparatus has been used to study the metabolism of frogs and other small animals.

Calorimeters have been constructed for the purpose of measuring, by the direct method, the heat production of larger animals and man. Usually, as in the case of the apparatus

shown in Fig. 273, they are designed to measure also the gaseous exchange of the subject (indirect calorimetry). This is a valuable provision, for it permits a comparison of the two methods. For the present, we are concerned only with that part of the design involved in the direct measurement of heat production. For this the arrangement is such that the subject may occupy a thermally insulated chamber in which heat lost from the body by radiation and conduction (about three-fourths of the total lost) is removed by a stream of cold water flowing through tubes attached to the inner walls. The number of Calories thus lost by the subject can easily be calculated from the volume of water passing through and the difference in temperature of the ingoing and outgoing water. The change in temperature of the water in degrees Centigrade multiplied by the volume of water in liters gives the Calories carried away from the apparatus during the period. This plus the heat value of the water vaporized from the body of the subject gives the total heat elimination. Any other loss of heat from the calorimeter is prevented by a double copper wall surrounding the chamber. These copper walls are connected with thermocouples so that an electric current is generated when any

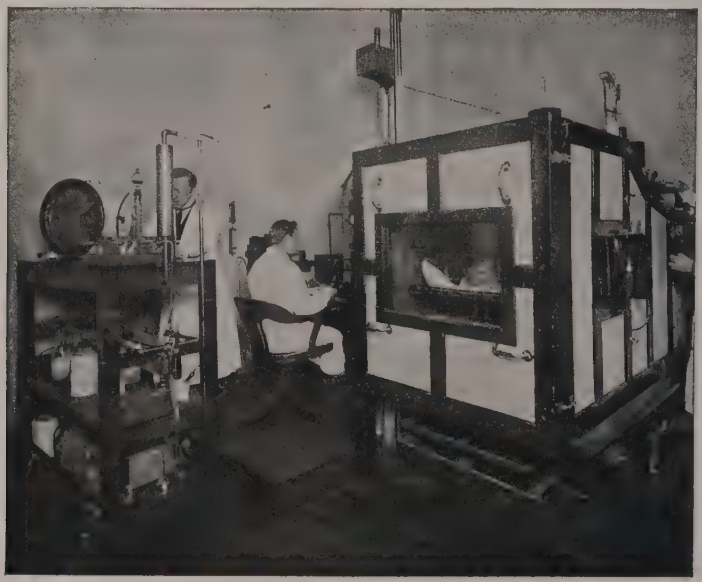


Fig. 273.—Respiration calorimeter of the Russell Sage Institute of Pathology, Bellevue Hospital, New York. At the left is seen the table with the absorption tubes; and in the middle, at the back, the electric control table for regulating the temperature of the double walls of the calorimeter. (Lusk's Science of Nutrition.)

difference in temperature occurs between the walls. If there is a change, temperature equilibrium is restored by passing cold water through coils or by electrical heating. In this manner the two walls are kept at the same temperature and consequently there can be no flow of heat between them. The heat used in vaporizing water from the skin and lungs is measured by collecting the moisture in a sulfuric acid bottle placed in the ventilating circuit and then multiplying its weight in grams by the heat of vaporization of water. At 20° C. the heat of vaporization is 0.586 Calorie per kilogram of water. A factor which must be taken into consideration is the temperature of the subject. Any change in this is noted and multiplied by the specific heat of animal tissue (0.83). If, for example, the temperature of a man weighing 70 kilograms varies one degree, there would be a change of 70 × 0.83 or 58.1 Calories in the heat given off. This calculation is made on the assumption that the temperature change is uniform throughout the body of the subject. The calorimeter used by Du Bois con-

tains a comfortable bed, windows, shelf, telephone, fan, electric light, and stethoscope. The larger calorimeters constructed by Benedict and Atwater contain, in addition, a stationary bicycle for the determination of the heat production during work. The subjects may remain in such chambers as long as twenty-four hours. The expense of installation and maintenance of calorimeters and the time needed for their operation are so great that the direct method is used in only a few institutions. The indirect methods are more widely employed for clinical work and physiological experimentation.

Indirect Methods

There are two general indirect methods for the study of metabolism, the "closed circuit" and the "open circuit" types.

The Closed Circuit Method.—In this the expired air is passed through bottles containing suitable reagents for the absorption of water and carbon dioxide, and the amount of oxygen used is determined from the amount added during the experiment to keep the total

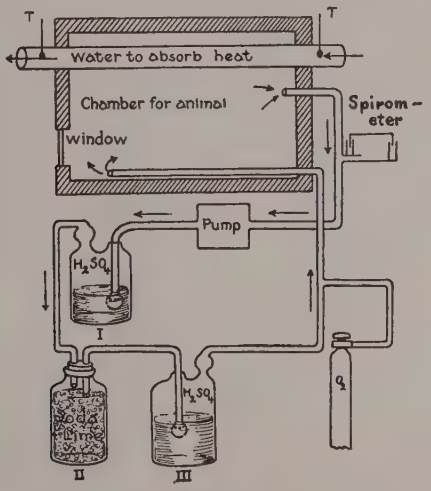


Fig. 274.—Diagram of Atwater-Benedict respiration calorimeter. As the animal uses up the O_2 the total volume of air decreases. This change is indicated by the spirometer, and a corresponding amount of O_2 is delivered from the weighed O_2 cylinder. The increase in weight of bottles II and III gives the CO_2; that of I, the water vapor.

volume of the system unchanged. This method may be used with a calorimeter (Fig. 274) in which case the results of the indirect method may be compared with those of the direct. The chamber is connected with a closed system of tubes through which air is passed by a pump. Outside the chamber the air passes through a spirometer, a bottle of concentrated sulfuric acid, a bottle of soda lime, and a second bottle of sulfuric acid. The first sulfuric acid absorbs water vapor in the air coming from the chamber, the soda lime takes out the carbon dioxide, and the second sulfuric acid takes up the water produced by the reaction between the soda lime and the carbon dioxide. The amounts of water and carbon dioxide given off by the subject are found by weighing these bottles before and after the subject has been placed in the chamber. During the experiment oxygen is admitted to the system from a side tube at such a rate that the amount used by the subject is exactly replaced. The quantity of oxygen taken up by the subject may be determined by weighing the cylinder from which it comes before and after the experiment or by passing the gas through a sensitive meter placed between the oxygen tank and the tubing of the system.

To avoid the necessity of building a closed cabinet for these determinations, numerous devices, such as the Benedict helmet, masks, mouthpieces and nosepieces, have been designed for connection of the subject with the apparatus. These contrivances are also used with the open circuit method.

The Open Circuit Method.—In this the subject breathes through a valve system so arranged that it separates the inspired from the expired air. The volume of expired air is measured by collecting it in a spirometer (Tissot method) or a rubber bag (Douglas method). A sample of the expired air is analyzed for carbon dioxide and oxygen and by suitable calculation the total respiratory exchange is obtained.

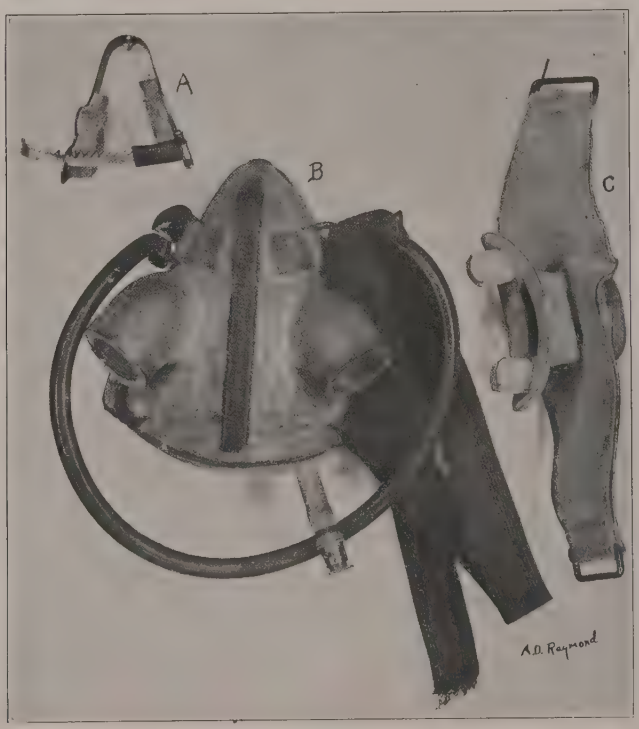


Fig. 275.—*A*, Nose clip; *B*, Face mask; *C*, Mouthpiece.

Description and Purposes of the Parts of the Apparatus Used: Valves, Mouthpieces, and Masks.—The various devices for connecting the subject with the apparatus are shown in Fig. 275. The mouthpiece (*C*) has a rubber flange, which fits between the subject's cheeks and teeth, and two soft rubber projections which are to be held between the teeth. The nose clip (*A*) is used to avoid any loss of air through this passage. Some individuals find it very difficult to breathe through a mouthpiece. Numerous types of masks and the Benedict helmet[46] are useful in such cases. Masks have the advantage that they allow the subject to breathe normally through the nose, but possess the disadvantages of being subject to leaks and of becoming uncomfortable during prolonged experiments. A diagram of the mask used by Bailey[60] and its connections with a spirometer are shown in Fig. 276.

The types of valves which have been designed to separate the inspired from the expired air are numerous. Such a valve should have low resistance to the passage of air so that the

subject will not experience a feeling of pressure. Further, the dead space should be small to avoid accumulation of carbon dioxide. The valve used in the Johns Hopkins Physiological Laboratory is a modification of the Lovén type; it is shown in Fig. 277. On inspiration the rubber membrane is pulled away from the metal ring, *A*, while the other membrane is pulled against a similar ring, *B*, on the other side. This arrangement allows air to pass from the atmosphere into the valve during inspiration and prevents atmospheric air from passing out through the expiratory side of the valve. On expiration the rubber membrane is pushed away from *B* while on the inspiratory side the membrane is brought into close contact with *A*. In this manner the inspired and expired airs are separated. The disadvantage of these valves is that the rubber may stick to the metal and break easily. Flutter valves such as are used in gas masks are more satisfactory for long experiments and for clinical use.

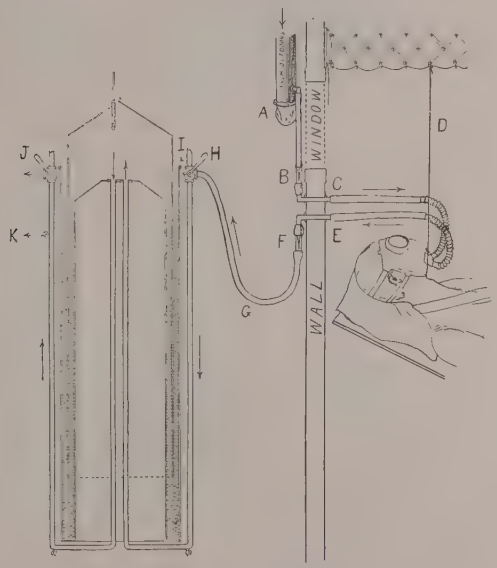


Fig. 276.—Apparatus for the determination of the basal metabolism. The subject, lying at rest on a cot and wearing a face mask, is separated by a wall and window from the spirometer. *C* and *E* are pipes leading from the mask to outside air and spirometer, respectively; *B* and *F* are flutter valves which direct inspiratory air to mask from outside and expiratory air to spirometer from mask. The spirometer consists of a bell which is arranged to rise freely as the expired air is collected under it. The entire dead space of the apparatus can be flushed out with expired air by allowing it to escape through the valve *J*. On closing this valve the expired air is caught in the spirometer bell. *H* is a valve which permits expired air to escape through *I*, a vent. (From Bailey: J. Lab. and Clin. Med. **6**: 657, 1921.)

The Collection of Expired Air.—The expired air may be collected in a spirometer or in a Douglas bag[75] or it may be measured directly by passage through a gas meter. Since ordinary gas meters are not sensitive enough to follow the sudden change in flow occurring at expiration, special meters have been designed which record and measure such changes with sufficient accuracy. Nevertheless the most practical method is to collect the expired air in a spirometer. A diagrammatic representation of a spirometer is given in Fig. 276. In the design of this apparatus special attention should be given to the freedom of movement of the bell, for its rise must be directly proportional to any increase in volume. The dead space must be small so that the amount of gas present at the beginning of the experiment does not influence the final composition of the gases in the spirometer. This factor may be minimized by washing out the spirometer with expired air before each experiment. The necessary compensation for the change in the buoyancy effect as the bell changes its position in the water is accomplished by attaching a weight to a spiral so that the pull on the bell varies with its

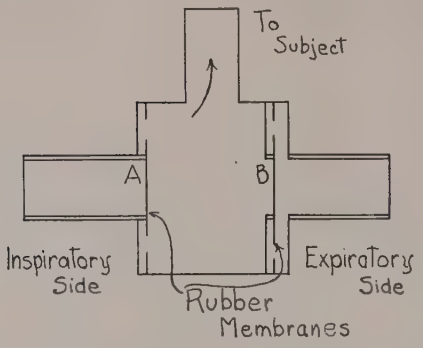


Fig. 277.—Respiratory valve. For description see text.

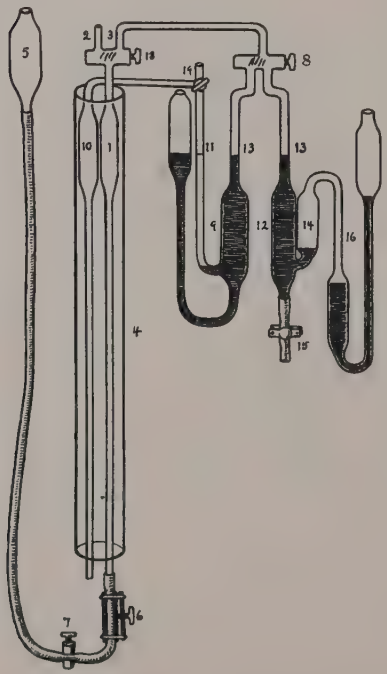


Fig. 278.—Haldane gas analysis apparatus. *1*, calibrated burette; *2*, side tube for admission of sample; *3*, connection to KOH and pyrogallate reservoirs; *4*, water jacket for temperature control; *5*, mercury reservoir; *6*, clamp for fine adjustment of mercury column; *7*, stopcock; *8*, stopcock for directing gas into KOH or pyrogallate reservoir; *9*, KOH reservoir; *10*, compensating burette; *11*, mark on tube for fixing volume of gas in compensating burette; *13*, marks on tube for volume control in KOH and pyrogallate reservoirs; *12*, *14*, *15*, *16*, pyrogallate reservoir.

position. Spirometers may be calibrated by passing air through an accurate meter into the bell, or by measurement of the circumference and height and calculating the volume.

One disadvantage of the spirometer is that it is not portable. The Douglas bag[75] was designed for use in experiments involving exercise such as walking or running. The bag is made of rubber, covered with canvas, and usually has a capacity of about one hundred liters. After collection of the gas its volume is measured by passing it from the bag through a meter. The disadvantages of the Douglas bag are that it wears out quickly and becomes permeable to carbon dioxide and oxygen. A slow leakage of gas may not be of significance when determinations are made immediately after a collection, but if the gas is allowed to remain in the bag for several hours serious error may result. The bag should be rolled tightly before and after each analysis.

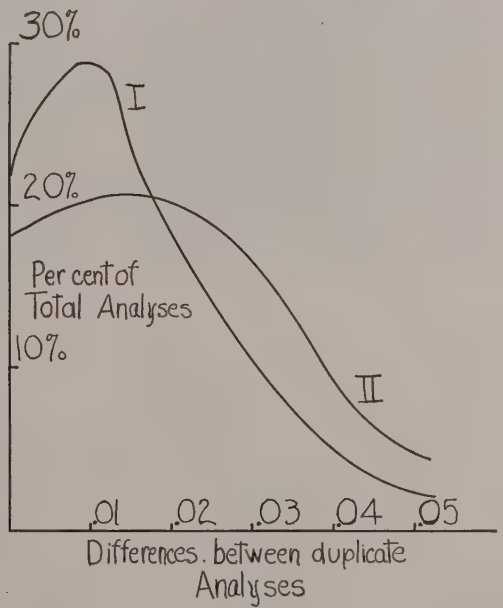


Fig. 279.—Deviation between duplicate analyses in terms of CO_2 (I) and O_2 (II) percentages plotted against the per cent of the total number of analyses. (From Gemmill: Am. J. Physiol. 98: 135, 1931.)

Gas Analysis.—After a period of collection a sample of expired air is analyzed. The type of gas analyzer most generally used is some modification of the Haldane apparatus (Fig. 278). This consists of a calibrated burette attached by stopcocks to two reservoirs, one containing a solution of KOH for the absorption of CO_2 and the other an alkaline pyrogallate solution for the absorption of O_2. A control tube is connected to the alkali reservoir to compensate for any changes in temperature or barometric pressure. To begin an analysis, gas is transferred from a sampling tube to the apparatus and its volume measured. The gas is then passed through the KOH solution several times and returned to the calibrated burette where its volume is again measured. The change in volume gives the amount of CO_2 in the original sample of gas. In a similar manner the O_2 is taken up in the pyrogallate solution and the resulting loss in volume determined. No analysis of expired air should ever be made without first testing the apparatus by analyzing a sample of atmospheric air. The results of duplicate analyses should agree within 0.03 per cent. Variations found in a series of 240 analyses are shown in Fig. 279. Exact details and practical suggestions for carrying out gas analyses may be found in the book by Peters and Van Slyke.[61]

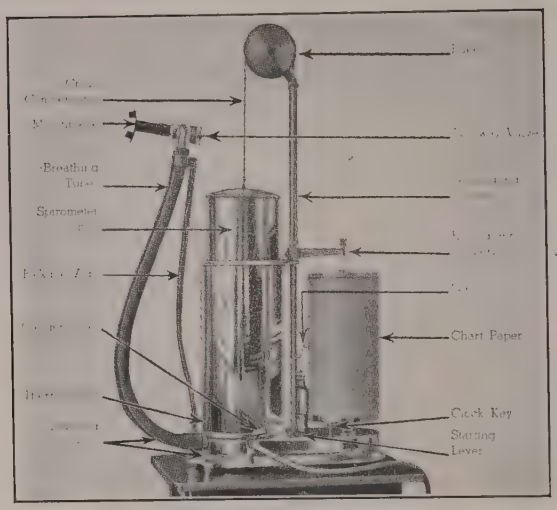


Fig. 280.—The Benedict-Roth metabolism apparatus. (Courtesy of Warren E. Collins, Inc., Boston.)

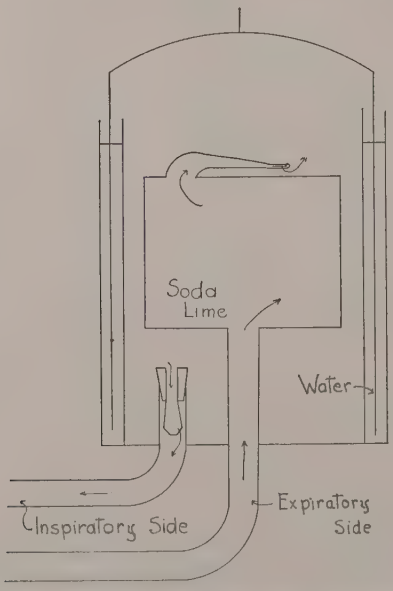


Fig. 281.—Diagram of the connections in the spirometer of the Benedict-Roth apparatus.

Clinical Methods.—The methods described above require considerable training and experience before satisfactory results are obtainable. For this reason simpler methods have been devised for clinical work. A type of apparatus widely used in hospitals and by physicians in their offices is shown in Fig. 280. It consists of a closed circuit from which oxygen is removed by the subject's lungs and in which the carbon dioxide of the expired air is taken up by passage over soda lime (Fig. 281). Before beginning an experiment an amount of oxygen is admitted sufficient to raise the spirometer bell to the zero mark on a vertical scale calibrated in terms of volume. The inspirations and expirations of the subject are reflected in alternate downward and upward movements of the spirometer bell, but these occur at a steadily decreasing height as the total volume of the system diminishes with the consumption of oxygen. The difference in the height of the bell at the beginning and the end of the run (usually six minutes) represents the volume of oxygen used in the interval. This is then corrected for aqueous tension and reduced to standard temperature and pressure. A graphic record of the breathing movements along a base line, which slants because of the fall in volume in the system, is usually made on graph paper from which the rate of oxygen consumption can be converted to Calories per hour. This method has several disadvantages. The assumption is made that the respiratory quotient is normal (0.82), and it is on this basis that the Calories are calculated. Such a procedure, however, does not introduce a large error, for the caloric value of one liter of oxygen varies but little for respiratory quotients between 0.70 and 1.00. A more serious criticism is that the accuracy of the determination depends on the regular breathing of the patient. It is very difficult for some individuals to breathe normally through a mouthpiece and valves, but with repeated trials a smooth slope is usually obtained for calculating the change in volume due to the oxygen consumption. With an apparatus of this type Benedict obtained values of 247, 245, and 241 ml. of oxygen in three successive trials on the same individual.

It is difficult to check the accuracy of the indirect methods. In the direct method alcohol is burned in the calorimeter and the heat produced is compared with the theoretical value calculated from the heat of combustion. Benedict[43] has devised a special alcohol combustion apparatus for testing the indirect methods. If this apparatus is not used, repeated tests carried out on a trained subject will give a good indication of the accuracy of the apparatus.

A critical comparison of the various indirect methods was made by Carpenter.[50] He concluded that the Benedict apparatus has two advantages: rapidity of operation and the fact that it gives a graphic record of the metabolism. The Tissot spirometric apparatus is not difficult to use and the results obtained with it are reliable. The Douglas bag method must be carefully controlled by testing the bags for diffusion of gases. Its chief advantage is the portability of the apparatus. For one who has mastered gas analysis, the Tissot spirometer is the apparatus of choice. If two spirometers are available they may be connected by valves so that one is filling while the other is being emptied. This permits continuous observations of metabolism over long periods of time (Gemmill[79]).

THE RESPIRATORY QUOTIENT

The respiratory quotient (R. Q.) is defined as the ratio of the *volume* of carbon dioxide expired to the *volume* of oxygen consumed during the same period of time. It has long been known that among animals this ratio varies to some extent with the food. The quantity of oxygen required and the amount of carbon dioxide produced in the combustion of food, either within or outside the body, depends on the chemical composition of the material. Therefore the respiratory quotient for any individual foodstuff may be determined from the equation representing its oxidative breakdown to the final products. Since equal volumes of gases at the same temperature and pressure contain the same number of molecules (Law of Avagadro), it is not necessary, in making this determination, to convert the number of molecules of the two gases into volumes. The following examples illustrating the method of calculating the respiratory quotient are taken from Lusk's *Science of Nutrition*.[60]

1. **Carbohydrate.**—The general formula for this class of foodstuffs may be written $(CH_2O)_n$ from which it is plain that hydrogen and oxygen are always

present in the proportions to form water. Therefore on combustion extramolecular oxygen is required only for the formation of carbon dioxide. That the respiratory quotient will be unity is evident from the following equation:

$$\underset{\text{(glucose)}}{C_6H_{12}O_6} + 6O_2 = 6CO_2 + 6H_2O$$

$$\text{R. Q.} = \frac{6 \text{ volumes } CO_2}{6 \text{ volumes } O_2} = 1.00$$

2. **Fat.**—In the oxidation of this substance, extramolecular oxygen is required not only for the oxidation of carbon but also for the oxidation of hydrogen. For this reason the respiratory quotient will be less than unity. If we take as an example tripalmitin, $C_{51}H_{98}O_6$, this fact becomes evident from the following equation:

$$2C_{51}H_{98}O_6 + 145\ O_2 = 102\ CO_2 + 98H_2O$$

$$\text{R. Q.} = \frac{102 \text{ volumes } CO_2}{145 \text{ volumes } O_2} = 0.703$$

Food fats, which are composed chiefly of the glycerides of palmitic, stearic, and oleic acids, give a quotient of 0.706.

3. **Protein.**—It is more difficult to calculate the respiratory quotient of the combustion of protein in the body because some of the oxygen and carbon of the constituent amino acids remains combined with nitrogen and is excreted as nitrogenous compounds of the urine and feces. Determinations have been based on accurate analyses of the ingested protein and of the excreta. Table XXXII gives the figures reported by Loewy:

TABLE XXXII

	ELEMENTS IN GRAMS				
	C	H	O	N	S
100 grams meat protein contain	52.38	7.270	22.68	16.65	1.02
Elimination:					
In the urine	9.406	2.663	14.099	16.28	1.02
In the feces	1.471	0.212	0.889	0.37	
Leaving for respiratory processes	41.50	4.40	7.69		
Intramolecular water		0.961	7.69		
For oxidation	41.50	3.439			

(From Lusk[60] after Loewy)

The quantities of carbon and hydrogen involved in oxidative processes require 138.18 grams of oxygen; 152.17 grams of carbon dioxide are produced. Converting these quantities into volumes* we find that the ratio for protein is:

$$\text{R. Q.} = \frac{77.52 \text{ liters } CO_2}{96.70 \text{ liters } O_2} = 0.802$$

4. **Other Substances.**—In a similar manner respiratory quotients have been calculated for the oxidation of a number of compounds of biological significance.

The actual calculation of the *total* and *nonprotein* respiratory quotients in a human subject is given on pages 736-739.

Significance of the Respiratory Quotient.—From the foregoing discussion it might seem that the determination of the respiratory quotient furnishes in-

*Conversion is carried out on the basis of the fact that at N. T. P. 1 gram of O_2 occupies 0.6998 liter, 1 gram of CO_2 0.5094 liter.

TABLE XXXIII

RESPIRATORY QUOTIENTS CALCULATED FROM CHEMICAL EQUATIONS FOR OXIDATION (RICHARDSON[62])

SUBSTANCE	R. Q.
Glycerol	0.86
Glyceric aldehyde	1.00
β-hydroxybutyric acid	0.89
Acetoacetic acid	1.00
Acetone	0.75
Lactic acid	1.00
Pyruvic acid	1.20
Alcohol	0.667

formation concerning the kind of foodstuff being metabolized. Such indeed is the general impression. Unfortunately experimental evidence has not given this idea complete support, especially when the metabolic changes have been examined over short periods of time. The difficulty arises from the fact that the cells of the body are able not only to oxidize various foodstuffs concurrently but also to convert one food material into another.

Theoretically, the ingestion of glucose should raise the respiratory quotient to 1.00 if glucose alone is oxidized. Benedict and Higgins[70] fed various amounts of sugar to fasting subjects. After the subject had ingested six hundred grams of glucose in one day, the highest respiratory quotient which they observed was 0.87. Cathcart and Markowitz[73] studied the change in the respiratory quotient and the increase in metabolism following the ingestion of various sugars. Glucose and maltose raised the metabolism, but the respiratory quotient did not reach unity. On the other hand, cane sugar raised the quotient to 1.00, but did not change the metabolism. Krogh and Lindhard[83] fed a group of men high carbohydrate or high fat diets over periods of two or more days. They observed that the respiratory quotient rose on a carbohydrate diet and fell on a fat diet, but it did not reach the theoretical levels, 1.00 and 0.71, respectively. Higgins[81] determined the quotient before and after ingestion of alcohol. Although the theoretical quotient for the oxidation of this substance is 0.667, the lowest figure obtained experimentally was 0.775. These facts illustrate the point that, even when the subject is on a diet consisting of a single chemically pure substance, oxidation of that substance to the exclusion of all others never occurs. Another complication is the transformation of food materials from one form to another. The conversion of carbohydrate to fat (which certainly occurs) tends to raise the quotient above unity, while the reverse process (which probably occurs) tends to lower it below 0.71. Soskin[91] has presented several lines of evidence which show that a quotient of 0.70 does not indicate inability to oxidize carbohydrate. His latest results were obtained in a study of the disappearance of sugar from the blood of fasting and fed dogs after evisceration. The fall in blood sugar followed the same curve in the fasting as in the fed dogs. He concluded that the utilization of sugar is not impaired by fasting and that the low respiratory quotients observed under such conditions are due to increased formation of carbohydrate and not to an exclusive oxidation of fat. This problem will be discussed more fully in Chapter L. The splitting off of CO_2 from acids or the taking up of oxygen by hydrogen released in the partial oxidation of a compound are reactions which may further complicate the calculation of the respiratory quotient.

Other things than oxidative processes exert profound effects on the value of the respiratory quotient. These may be summarized as follows (Richardson[62]):

A. The respiratory quotient is increased by:
   1. Hyperventilation
   2. Acid formation
      a. Lactic acid (muscular exercise; convulsions; asphyxia; adrenalin)
      b. Keto-acids (diabetes; carbohydrate starvation)
   3. Acid retention (as in nephritis)

B. The respiratory quotient is decreased by:
   1. Hypoventilation
   2. Acid removal (by oxidation, excretion of free acid, synthesis, loss of HCl from stomach by vomiting)
   3. Alkalosis produced by alkali therapy.

In view of the evidence presented above the respiratory quotient should not be regarded as an exact indicator of specific metabolic processes, but as a resultant of all the changes in the body which require oxygen and lead to excretion of carbon dioxide. In metabolism experiments, however, it is necessary to convert liters of oxygen into Calories. Zuntz and Schumburg constructed tables (for their latest modification see Lusk[84]) which give, for different respiratory quotients, the caloric value of a liter of oxygen. The assumption underlying these figures is that a nonprotein respiratory quotient (see page 739) of 1.00 indicates an exclusive oxidation of carbohydrate while one of 0.71 signifies an oxidation of fat alone, and any quotient between these two values is the resultant of the burning of a mixture of fat and carbohydrate in definite proportions. The situation has been shown to be more complex than this simple theory demands. The question arises as to what should be used for the conversion of liters of oxygen to calories. The answer is that it does not make much difference. At a respiratory quotient of 0.71 the number of Calories produced per liter of oxygen used is only about 6 per cent less than when the respiratory quotient is 1.00. In the following section this fact is illustrated by an example (page 739).

The Calculations

The calculations required in the determination of the energy exchange by the indirect method are given in the following example.

Analysis of Expired Air.—

Carbon dioxide:

1st reading of burette	20.00
2nd reading (after absorption)	19.20
CO_2 absorbed	0.80

$$\frac{0.80}{20} \times 100 = 4.0\%\ CO_2 \text{ in expired air}$$

Oxygen:

2nd reading of burette	19.20
3rd reading (after absorption)	15.90
O_2 absorbed	3.30

$$\frac{3.30}{20} \times 100 = 16.5\%\ O_2 \text{ in expired air.}$$

Determination of Respiratory Quotient.—

O_2 in atmospheric air = 20.94%
$O_2 + CO_2$ in expired air (16.5 + 4.0) = 20.50%
N_2 in atmospheric air = 100 − 20.94 = 79.06%
N_2 in expired air = 100 − 20.50 = 79.50%

The change in the percentage of nitrogen, a gas which is inert in the body, means that there is a difference in the volumes of the inspired and expired air. This is due to the fact that during the experiment the carbon dioxide given off is less than the oxygen taken up. A correction must be made for this difference between the total volume of the inspired and expired air. Multiplying the ratio of the percentage of oxygen to the percentage of nitrogen in atmospheric air by the percentage of nitrogen in the expired air gives a corrected value for the oxygen percentage of the inspired air. The actual calculation, made on the basis of the figures appearing above, will make this clearer:

$$20.94 : 79.06 = x : 79.5$$

$$x = \frac{20.94}{79.06} \times 79.5 = 21.07$$

Since the ratio $\frac{20.94}{79.06}$ is constant for each experiment, a factor, 0.265, may be used in the multiplication. The calculation can be simplified by using the accompanying abbreviated table (Table XXXIV) which gives the O_2 figure corresponding to the various percentages of N_2 in the expired air.

TABLE XXXIV

THE PERCENTAGE OF OXYGEN WHICH IS EQUIVALENT TO THE NITROGEN FOUND IN THE EXPIRED AIR

To obtain the nitrogen in the expired air, add the percentages of CO_2 and O_2 found and subtract the sum from 100. The table gives the percentage for O_2 corresponding to this figure:

% N_2	78.7	78.8	78.9	79.0	79.1	79.2	79.3	79.4	79.5
% O_2	20.85	20.88	20.91	20.93	20.96	20.99	21.01	21.04	21.07

Having reduced both percentages to the same basis, a simple subtraction gives the percentages of carbon dioxide excreted and of oxygen used during the experiment:

Percentage of O_2 absorbed = 21.07 − 16.50 = 4.57%
Percentage of CO_2 excreted = 4.00 − 0.03 (CO_2 in inspired air) = 3.97%

Since the amount of CO_2 in the inspired air is so small it is not necessary to make a correction as in the case of the oxygen consumption. The respiratory quotient, the ratio of the volume of CO_2 given off to the volume of oxygen used, is therefore,

$$\frac{3.97}{4.57} = 0.87$$

Total Gas Exchange.—Let us suppose that the volume of air expired in fifteen minutes into the Tissot spirometer is 100 liters at 20° C. and 747 mm. Hg (brass-scale barometer). This volume must be corrected to give the volume of dry air at 0° C. and 760 mm. Hg. To do this, the following corrections must be made:

1. The pressure due to water vapor must be subtracted from the observed barometric pressure (Table XXXV gives these corrections at various temperatures).

TABLE XXXV

TENSION OF AQUEOUS VAPOR IN MILLIMETERS OF MERCURY

To obtain the dry barometric pressure, subtract the mm. Hg corresponding to the temperature of the air from the barometric pressure at the time of the experiment:

Temp.	15°	16°	17°	18°	19°	20°	21°	22°	23°	24°	25°
Mm.	12.79	13.64	14.54	15.49	16.49	17.55	18.67	19.84	21.09	22.40	23.78

2. The barometric readings must be corrected for temperature as the barometer alters its length with changes in temperature (Table XXXVI).

TABLE XXXVI

TEMPERATURE CORRECTIONS TO REDUCE READINGS OF A MERCURIAL BAROMETER WITH A BRASS SCALE TO 0° C.

Subtract the appropriate quantity as found in the table from the height of the barometer. The table is for a barometer with a brass scale; the values are a little lower (about 0.2 mm.) than for the glass scale. The corrections for intermediate temperatures can be approximated by interpolation:

Temp. °C.	740 mm.	750 mm.	760 mm.	770 mm.	780 mm.
15	1.81	1.83	1.86	1.88	1.91
20	2.41	2.44	2.47	2.51	2.54
25	3.01	3.05	3.09	3.13	3.17

In this experiment, with the expired air and the barometer at 20°, the correction for the vapor tension is 17.55 mm., for the expansion of the brass scale of the barometer 2.43 mm. Therefore the corrected barometric pressure is:

$$747 - (17.55 + 2.43) = 727.02 \text{ mm.}$$

To correct the volume to 0° C. and 760 mm. pressure, the following formula may be used:

$$V\ (0° \text{ and } 760 \text{ mm.}) = \frac{P\ V}{(1 + 0.00367\ t)\ 760},$$

where P is the corrected barometric pressure, V the observed volume, t the temperature and 0.00367 the coefficient of expansion of gas. In practice, however, tables are used which give this factor for various pressures and temperatures. Carpenter[51] has published such

TABLE XXXVII

FACTORS FOR REDUCING GASEOUS VOLUMES TO NORMAL TEMPERATURE AND PRESSURE*

The observed volume, when multiplied by the factor corresponding to the temperature and corrected pressure, will give the volume of the expired air reduced to 0° and 760 mm.

Mm.	15°	16°	17°	18°	19°	20°	21°	22°	23°
750	0.919	0.915	0.911	0.907	0.902	0.898	0.893	0.889	0.884
760	0.932	0.928	0.923	0.919	0.915	0.910	0.906	0.901	0.897
770	0.944	0.940	0.936	0.931	0.927	0.922	0.918	0.913	0.909

tables (Table XXXVII) together with others which aid in the calculation of metabolic rate. The calculated factor in this experiment is 0.892. Therefore,

$0.892 \times 100 = 89.20$ liters of dry air expired corrected to 0° C. and 760 mm. Hg.

The amount of oxygen consumed in fifteen minutes is

$$89.20 \times 4.57 = 4.08 \text{ liters of } O_2$$

and the amount of carbon dioxide given off is

$$89.20 \times 3.97 = 3.54 \text{ liters } CO_2$$

The Caloric Value Calculated From the Respiratory Metabolism.—The nonprotein respiratory quotient is calculated by deducting from the O_2 and CO_2 values of the total respiratory exchange the O_2 and CO_2 involved in the protein metabolism. In brief experiments it is impossible to measure the urinary nitrogen. Therefore, an assumption must be made on the

*These factors are obtained by the formula, $\frac{1}{1 + 0.00367\ t} \times \frac{P - e}{760}$, where t is the temperature, P the barometric pressure after scale correction and e the pressure of aqueous vapor at temperature t.

basis of the amount of nitrogen excreted in twenty-four hours. Suppose, for example, that 14.4 grams of nitrogen are excreted in that time; the average hourly output is 0.6 grams. It has been determined that, for every gram of urinary nitrogen derived from protein, 8.49 grams of O_2 are used and 9.35 grams of CO_2 are eliminated. Using these values and the factors for converting grams of CO_2 and O_2 into liters (1 gram CO_2 = 0.5094 liters and 1 gram O_2 = 0.6998 liters), the amount of CO_2 given off and O_2 required for the oxidation of protein may be calculated as follows:

$$0.6 \times 9.35 \times 0.5094 = 2.86 \text{ liters of } CO_2 \text{ per hour}$$
$$0.6 \times 8.49 \times 0.6998 = 3.56 \text{ liters of } O_2 \text{ per hour}$$

Taking the total amount of oxygen used and of carbon dioxide given off per hour and subtracting the values obtained for the oxidation of protein, the amounts of the respiratory gases involved in the nonprotein oxidation are obtained as follows:

$$(4 \times 3.54) - 2.86 = 11.30 \text{ liters of } CO_2 \text{ per hour}$$
$$(4 \times 4.08) - 3.56 = 12.76 \text{ liters of } O_2 \text{ per hour}$$

Thus the nonprotein respiratory quotient is $\frac{11.30}{12.76}$ or 0.88.

TABLE XXXVIII

CALORIC VALUE OF 1 LITER OF OXYGEN AT VARIOUS RESPIRATORY QUOTIENTS*

R. Q.	0.707	0.75	0.80	0.85	0.90	0.95	1.00
Calories	4.686	4.739	4.801	4.862	4.924	4.985	5.047

From Table XXXVIII it is seen that at a quotient of 0.87 one liter of oxygen is equivalent to 4.887 Calories; at a respiratory quotient of 0.88 this value is 4.899 Calories. If the respiratory quotient were not determined but assumed to be 0.82, the value would be 4.825. Using these values and the fact that 1 gram of urinary nitrogen is equivalent to 26.51 Calories, the results shown in Table XXXIX are obtained:

TABLE XXXIX

RESPIRATORY QUOTIENT		CALORIES PER HOUR	CALORIES PER SQ. METER OF BODY SURFACE PER HOUR	BASAL METABOLIC RATE
Total	0.87	79.76	39.88	+1.0
Nonprotein	0.88	78.42	39.21	−0.8
Assumed	0.82	78.82	39.41	−0.2

CALCULATION OF THE BASAL METABOLIC RATE

For reasons to be discussed it is customary to calculate the metabolism on the basis of Calories per square meter of body surface per hour and to compare this value with a normal standard. Assuming that a subject weighs 80 kilograms and is 180 centimeters in height, his surface area, as obtained from the chart constructed by DuBois (Fig. 283), is 2.0 square meters. From the table of standard metabolic rates (Table XL), it is found that a man between twenty and thirty years of age should have a metabolism of 39.5 Calories per square meter of body surface per hour. The observed value is then divided by the factor and expressed as a percentage, from which one hundred is subtracted algebraically to give the metabolic rate. There is practically no difference between the metabolic rates obtained from the three determinations in

*Calories $= 4.686 + \frac{(\text{R. Q.} - 0.707) \times 0.361}{0.293}$ (Lusk[60])

which different respiratory quotients are employed (see Table XXXIX). Since normal individuals vary ± 15 per cent from the standard, the variation due to the method of calculation is very small. It would be well, especially in short

TABLE XL

CALORIES PER SQUARE METER OF BODY-SURFACE (HEIGHT-WEIGHT FORMULA) PER HOUR (Aub and DuBois Standards)

AGE (YEARS)	MALES	FEMALES
14 to 16	46.0	43.0
16 to 18	43.0	40.0
18 to 20	41.0	38.0
20 to 30	39.5	37.0
30 to 40	39.5	36.5
40 to 50	38.5	36.0
50 to 60	37.5	35.0
60 to 70	36.5	34.0
70 to 80	35.5	33.0

determinations, to disregard the Zuntz-Schumburg tables with their implication that a given respiratory quotient means the oxidation of a definite mixture of carbohydrate and fat. It is preferable to assume an average caloric value for this determination.

Comparison of Direct and Indirect Methods

It was necessary to discuss methods and the respiratory quotient before continuing the consideration of the application of the first law of thermodynamics to biological systems. According to this law the heat produced by the combustion of food material should be equivalent to the heat liberated by the subject at rest. Rubner[89] in 1894 determined by means of a calorimeter the heat produced by dogs and at the same time measured the carbon dioxide expired and the nitrogen excreted in the urine. Assuming that under fasting conditions a dog oxidizes only protein and fat, he was able to calculate the amount of food material burned in twenty-four hours. By comparing the heat available from the oxidation of this material with the actual amount of heat liberated by the animal during the same period of time, he found close agreement between these two observations on fasting dogs and also on dogs which were fed meat and fat. His results are given in Table XLI.

TABLE XLI

COMPARISON OF HEAT CALCULATED FROM GASEOUS EXCHANGE WITH HEAT ACTUALLY PRODUCED (Rubner[89])

FOOD	DAYS	HEAT CALCULATED CALORIES	HEAT DETERMINED CALORIES
Starvation	5	1296.3	1305.2
	2	1091.2	1056.6
Fat	5	1510.1	1495.3
	6	2249.8	2276.9
Meat	7	4780.8	4769.3

From these results Rubner was able to compare the heat produced during the oxidation of one gram of protein or fat in the body with that liberated when the same amount of material was burned in a bomb calorimeter (Table XLII).

TABLE XLII

A COMPARISON OF THE HEATS OF COMBUSTION OF ONE GRAM OF FOOD MATERIAL IN THE ANIMAL BODY AND IN A CALORIMETER

FOOD	HEATS OF COMBUSTION OF ONE GRAM IN CALORIES	
	IN ANIMAL BODY	IN THOMPSON CALORIMETER
Meat	4.059	4.000
Meat	4.007	4.000
Fat	9.334	9.423
Fat	9.353	9.423

Rubner's work was continued by Atwater and Benedict in this country. With the aid of Rosa, Atwater[67] constructed a calorimeter in which both the heat production and the respiratory metabolism of a human being could be measured. Some of their results are given in Table XLIII.

TABLE XLIII

COMPARISON OF INDIRECT AND DIRECT CALORIMETRY APPLIED TO HUMAN SUBJECTS AT REST AND AT WORK (Atwater[67])

TYPE OF EXPERIMENT	NUMBER OF EXPERIMENTAL DAYS	AVERAGE CALORIES PER 24 HOURS	
		INDIRECT CALORIMETRY	DIRECT CALORIMETRY
Rest	41	2246	2246
Work	66	4682	4676

During a series of feeding experiments on dogs Murlin and Lusk[86] also compared the indirect with the direct method of calorimetry. Their results are summarized in Table XLIV. Coleman and Dubois[74] extended this work to

TABLE XLIV

A COMPARISON OF THE DIRECT AND INDIRECT METHODS OF CALORIMETRY (Murlin and Lusk[86])

DOG	NUMBER OF EXPERIMENTS	METHOD		DIFFERENCE		NUMBER OF EXPERIMENTS IN WHICH ERROR WAS	
		INDIRECT (CALORIES CALCULATED)	DIRECT (CALORIES MEASURED)	CALORIES	%	UNDER 2%	OVER 2%
III	10	996.71	975.05	21.66	2.2	5	5
XIV	22	2244.20	2230.18	14.02	0.6	14	8

a study of typhoid fever patients and found that while the total Calories determined for all their subjects by the two methods checked very closely, the results of individual experiments deviated as much as 17 per cent.

From the examples given above it is apparent that the caloric content of food can be compared with the actual amount of heat liberated when the body metabolizes this food. This fact proves that the first law of thermodynamics holds for such a complex biological system as the human body. The slight deviations between the two quantities are probably due to the use of the Zuntz-Schumburg tables for the calculation of the caloric value of oxygen. Poulton[87] has critically examined the results of Benedict and Carpenter and has found that the percentage differences between the heat produced as calculated from the oxygen consumption and the actual heat as measured by the calorimeter

varied with the respiratory quotient. The graphic summary of this comparison is given in Fig. 282 which shows that the calculated heat production is too high for the lower respiratory quotients and too low for the higher ones. The variations are greater than the analytical error incurred in measuring the heat production and the respiratory quotient of the combustion of alcohol. Poulton suggests that these variations are due to fundamental errors in the Zuntz-Schumburg tables, since the latter do not allow for the conversion of carbohydrate to fat at the higher quotients nor for a possible transformation of fat to carbohydrate at the lower. The agreement between the calculated and the observed heat productions is at its best for the range of respiratory quotients usually found in basal metabolic tests. It is not surprising that relatively poor agreements are observed under abnormal conditions. For example, Benedict

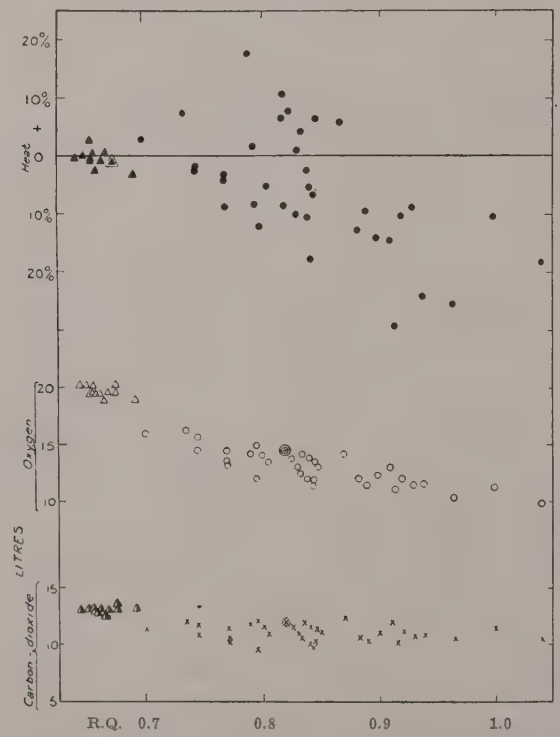


Fig. 282.—Discrepancies between the results of direct and indirect calorimetry at various respiratory quotients. The abscissae represent the respiratory quotients, and the horizontal line at zero, in the upper part of the figure, the measured heats (direct calorimetry). Satisfactory agreement between the two methods would require that the points lie more or less evenly above and below this line throughout the range of respiratory quotients.

● = the difference between the calculated and measured heats expressed as percentages of the latter.

▲ = values obtained from burning alcohol in the calorimeter.

▲ = carbon dioxide } alcohol checks
△ = oxygen }

○ = oxygen } values during the first day of fasting calculated per hour.
× = carbon dioxide } Subjects at rest.

The measured heat has been corrected both for change in body weight and body temperature. (From Poulton: Proc. Roy. Soc. Med. 26: 1591, 1933.)

and Carpenter[48] found that direct and indirect calorimetry do not necessarily agree when excessive amounts of carbohydrate are ingested.

Second Law of Thermodynamics.—Heats of combustion which are used at the present time in metabolic experiments do not give any information concerning that part of the heat, the free energy, which is available for work. Free energy may be greater or less than the heat of combustion. If greater than the heat of combustion, the process may be improved so that more work may be obtained from the system. If the free energy is less, even if all of this energy may be converted into work, there is still additional energy which is unavailable for work. These facts have been incorporated into the second law of thermodynamics which deals with this loss of availability of energy for external work. The application of this law enables the observer to decide whether a certain reaction can take place and to determine the maximal amount of work that may be obtained from the system. It tells nothing of the speed of the reaction nor of the mechanisms involved. At the present time, free energy data can be applied only to simple systems, such as enzyme reactions or bacterial metabolism. The application of free energy data to metabolic processes will continue as our knowledge of the data and of the metabolic changes increases. It may be that in this century the use of the second law of thermodynamics will lead the way to an advance in our knowledge of metabolic processes, comparable to that which resulted in the application of the first law of thermodynamics to biological problems in the last century.

BASAL METABOLISM

In order that a *comparison* of the metabolic activity of individuals and species may be made, certain conditions have been selected for its determination. DuBois[54] lists the many factors which influence metabolism as follows:

A. Factors excluded in all basal tests on normal controls:

1. Muscular movements during the test
2. Recent muscular exertion (within a half to one hour)
3. Food within twelve or fourteen hours
4. Strong emotions, noises, discomforts
5. Extremes of environmental temperature
6. Disease

B. Factors taken into account in the interpretation of determinations of basal metabolism:

Age	Athletic training
Sex	Climate
Weight and height	Altitude
Surface area	Sleep
Under- or overnutrition	Body temperature

C. Additional factors which may or may not be of importance:

Occupation	Vigorous exercise or emotion
Race	on day before the test
Previous diet	Novelty of the situation
Menstruation	Time of year

The three factors that have the most to do with determining the level of metabolism are muscular activity, extremes of external temperature, and digestion of food. If a subject is removed from the influence of these factors, the metabolism corresponds to the energy exchange for the minimal functional activity of the body. The term *basal metabolism* has been applied to the energy changes of the body under these conditions. It is usually determined twelve to fourteen hours after the last meal with the subject at rest and in a comfortable environmental temperature. Krogh has suggested the term *standard metabolism* for the heat production under these conditions since the metabolism can be lowered from the "basal" level by sleep or drugs. Benedict uses the term "postabsorptive" for the same reasons. The term *basal metabolism,* however, has taken a definite meaning and is commonly used in this country.

Surface Area.—Basal metabolism is reported in terms of Calories per square meter of body surface. Rubner established this empirical relationship by measuring the metabolism of dogs of various sizes and of other mammals varying in weight from 18 grams to 128 kilograms. His results are given in Table XLV.

TABLE XLV

RELATIONSHIP BETWEEN HEAT PRODUCTION AND BODY SURFACE (From Rubner[88, 89])

DOGS		VARIOUS MAMMALS		
WEIGHT IN KILOGRAMS	CAL. PER SQ. METER BODY SURFACE PER 24 HR.	ANIMAL	WEIGHT IN KILOGRAMS	CAL. PER SQ. METER BODY SURFACE PER 24 HR.
31.20	1036	Hog	128.00	1074
24.00	1112	Man	64.00	1042
19.80	1207	Dog	15.00	1039
18.20	1097	Guinea pig	0.50	1246
9.61	1183	Mouse	0.018	1185
6.50	1153			
3.19	1212			
Averages	1142			1145

It was later shown that Rubner's figures for the number of Calories per square meter of body surface were too high as compared to modern standards. The same relationship, however, holds for the revised values (Table XLVI).

TABLE XLVI

RELATIONSHIP BETWEEN HEAT PRODUCTION AND BODY SURFACE IN MEN (Rubner's Analysis of Material Taken From Benedict's Determinations[84])

NO. OF INDIVIDUALS	AVERAGE WEIGHT	VARIATION IN WEIGHTS	CALORIES PER SQ. METER BODY SURFACE
	kg.	kg.	per 24 hours
6	48.7	40-50	922
41	53.4	50-60	914
164	64.5	60-70	927
24	74.7	70-80	924
8	83.7	80-90	924
			Average 922

Is there any explanation for this relationship? In physical systems, the rate of cooling is dependent upon the area of the body and upon the difference in

temperature between the body and the surrounding atmosphere. This law does not apply to the body of a warm-blooded animal since the rate of heat loss is not changed in proportion to the temperature of the surrounding atmosphere. If it were, there would be no need for any heat production when the external temperature equals body temperature. Further, Harris and Benedict showed that a dog kept in their laboratory for several months had a decrease in metabolism of 19 per cent without any change in body surface. Benedict obtained similar results in studies on a man during starvation. In infants, the total metabolism is more nearly proportional to the body weight than to surface area. Obviously, it is not clear why there should be even a rough correlation between metabolism and body surface. In this connection it is of interest to note that vital capacity, cardiac output, and cross section of the aorta and trachea are also related to the surface area of the body.

Part of the difficulty in accepting the relationship between metabolism and surface area as a fact of fundamental significance arises from the inaccuracy of the measurement of the latter. In 1879, Meeh marked out in geometric designs the bodies of six adults and ten children. From these measurements, he derived the formula $S = KW^{\frac{2}{3}}$, where K is a constant for a given species. Rubner used this formula in his calculations of the surface areas of animals. Benedict[49, 50] has discussed critically the use of this formula. He points out that in the case of the rabbit 13 per cent of its body weight may be intestinal contents. It would introduce a large error to calculate surface area of a rabbit on a weight basis when so much of the weight is made up of metabolically inert material. The same problem arises in the case of ruminants where a large portion of the total body weight may be derived from intestinal contents. The exponent 0.666 has also been revised by various writers, some using a value as low as 0.53, others one as high as 0.80.

The most variable factor, however, has been the so-called constant K. Benedict[49] has evaluated this constant for a large number of laboratory animals. He describes the difficulties in measuring the surface areas of animals of simple geometric design, such as the snake. The actual measurement of the area of the skin after removal from a snake always gives a greater value than the calculated one in spite of all precautions to avoid stretching. Mitchell has shown in the case of the rat that the surface area depends on the position of the animal. Also, the values of K used by Rubner[64] varied from 4.62 for the frog to 18.6 for the snake. From a study of the more recent literature, and from his own determinations, Benedict has shown that the average value of K is close to 10 for all species.

The same difficulty arose when the Meeh formula was applied to man. DuBois and DuBois[76, 77] determined the surface area of a small group of individuals by measuring paper casts of their bodies. They derived a formula which was based on height and weight:

$$\text{S.A.} = W^{0.425} \times H^{0.725} \times 71.84$$

where S.A. is surface area in square centimeters, W is weight in kilograms, and H height in centimeters. This formula has been used to construct graphs from which the surface area of any individual may be determined when the height and weight are known (Fig. 283). Although they derived this general formula

from a study of a small group of individuals, other observers have determined the surface area of man and have found that this mathematical relationship does hold for a large number of individuals.

There are, therefore, two variables in the consideration of metabolism in man and animals. The metabolism itself can be determined very accurately by a large number of methods, while the surface area is more difficult to measure. The variability in surface area measurements no doubt accounts for the fact that the basal metabolism of some individuals differs widely from the accepted standards. Boothby and Sandiford analyzed the results of determinations of basal metabolic rates of 8,614 patients and found that 77 per cent of this group fell within ± 10 per cent of the normal standards and 90 per cent fell within ± 15. Thus, 10 per cent of this group fell outside the wider limits. It is customary, however, to consider ± 15 per cent the normal variation from the accepted standards of basal metabolism. Since these standards were derived from tests on patients, it is not surprising that individuals accustomed to metabolic tests should give results that are below these values.

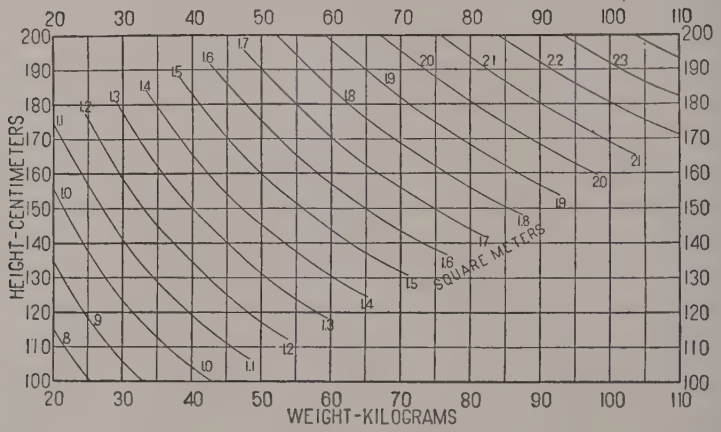


Fig. 283.—Chart for determining surface area of man in square meters from weight in kilograms (Wt.) and height in centimeters (Ht.) according to the formula: Area (Sq. Cm.) $= Wt.^{0.425} \times HT.^{0.725} \times 71.84$. (From DuBois and DuBois: Arch. Int. Med. 17: 863, 1916.)

Although "heat per square meter of surface area" does not represent a thermal law, it will be used for practical purposes until a better standard is obtained. Benedict[49] suggests that the emphasis should be shifted from a comparison of metabolism with heat loss to a consideration of the relationship of metabolism to heat production. This is the work of the future. He believes that the relationship between heat production and surface area is wholly fortuitous.

The various factors which affect basal metabolism were listed at the beginning of this chapter. Carpenter[52] has reviewed the magnitude of the changes due to several of these as follows:

Minor Muscular Movements.—The subject must remain perfectly quiet during the determination. Benedict and Benedict have determined the effect

of slight arm and leg movements, such as raising the hand to the forehead every few seconds, or crossing and uncrossing the legs every twenty seconds. In one individual the arm movements changed the metabolism from a basal value of 200 ml. oxygen to 210 ml. per minute, while the leg movements raised it to 222 ml. Therefore, movements such as these should be avoided. The subject should be placed in a comfortable position so that there will be no desire to change position during the determination. The usual motions of rising, dressing, and walking to the laboratory do not affect the basal values provided that the subject rests for thirty minutes before the test. On the other hand, after strenuous muscular exercise the metabolic rate may not return to the basal level for several hours (see page 842).

Temperature.—The subject must be in a room at a comfortable environmental temperature. In the course of his studies of cardiac output, Grollman[80] measured the metabolism of a subject exposed to temperatures ranging from

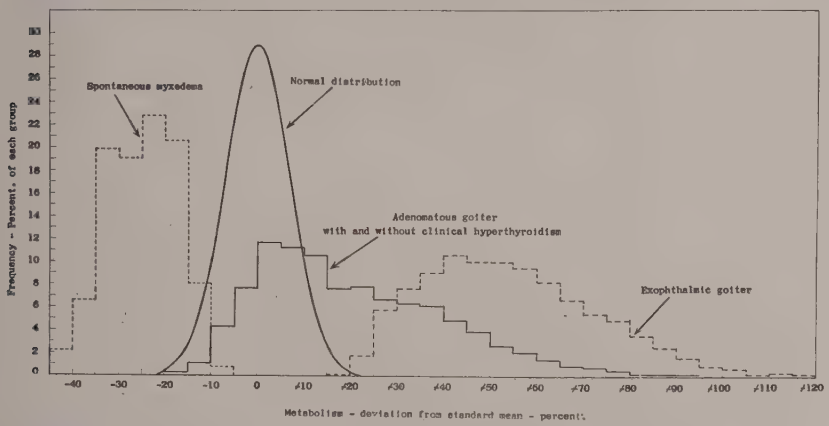

Spontaneous myxedema
Normal distribution
Adenomatous goiter
with and without clinical hyperthyroidism
Exophthalmic goiter
Frequency - Percent. of each group
Metabolism - deviation from standard mean - percent.
-40 -30 -20 -10 0 +10 +20 +30 +40 +50 +60 +70 +80 +90 +100 +110 +120

Fig. 284.—Basal metabolism in three thyroid diseases compared with group of normal individuals. Percentage frequency distribution for each group. (From Boothby, Berkson, Plummer: Ann. Int. Med. **11**: 1014, 1937.)

0° to 45° C. The metabolism at 0° was 330 ml. of oxygen; it decreased to 240 ml. at 30°, and then rose with increasing temperatures, reaching 260 ml. at 40°. The rise at the lower temperature is attributable to shivering and increased muscular tone. The gradual decline from 20° to 30° is due to greater muscular relaxation. The increase from 30° to 45° may be due to an increased reaction velocity of the chemical processes in the cells. It may also result, in part at least, from the increased activity of the sweating, respiratory and cardiac mechanisms. DuBois has calculated that the metabolism increases about 13 per cent for each degree rise of body temperature. It is, therefore, very important in metabolic experiments to record the temperature of the subject and of the room.

Age.—The standards given in Table XL are divided into various age groups. Very few persons, however, have been followed over long periods of time. Carpenter gives data on two individuals whose metabolism was followed over a period of twenty-four years. In one person, the metabolism fell from

27.8 Calories per kilogram per day to 23.5 Calories, while in the other subject, the change was less, from 22.5 to 20.6 Calories per kilogram per day. The metabolism of many more persons should be followed over long periods of time in order to obtain sufficient data on the effect of age.

Racial Variations.—Compared with American standards, natives in Yucatan have a higher metabolism (+8.4 per cent) while a group of female students at Madras, India, were found to have a much lower one (–17.4 per cent). A group of Chinese women living in America had an average metabolism 10.4 per cent below American standards. These few examples illustrate that there may be significant deviations in the metabolism according to race.

The effect of ingestion of food will be discussed in the separate chapters on proteins, fats, and carbohydrates. It is impractical to discuss in detail the many minor factors which may affect basal metabolism. Previous diet, novelty of procedure, climate, degree of muscular development, over- or under-nutrition may influence the metabolism slightly. For practical purposes, it is customary to take the lowest value obtained in a series of determinations; the majority of the factors mentioned above raise the metabolism.

Application of Basal Metabolic Studies to Clinical Conditions.—Since the introduction of standard methods of determination of basal metabolism and of adequate standards for comparison, many studies have been made on patients. The most practical result of this work has been the use of basal metabolic studies in aiding the diagnosis of doubtful cases of hypo- or hyperthyroidism. Boothby, Berkson and Plummer[72] have analyzed the percentage frequency distribution for thyroid diseases (Fig. 284). It may be seen from the figure that patients suffering from myxedema and exophthalmic goiter fall, with few exceptions, outside the normal group, but those with goiter are distributed between the normal and exophthalmic groups. In addition to an aid to diagnosis, basal metabolic tests can be used to obtain evidence concerning the value of medication in thyroid diseases and to determine the time for operation in the hyperthyroid cases.

Basal metabolic tests are also useful in cases of obesity and diabetes, for they aid the physician in understanding the nutritive condition of the patient and thus help him to prescribe an adequate diet. These tests have also been used as a postoperative procedure after the removal of the thyroid gland in cardiac cases. Since there is a relationship between metabolic rate and cardiac work, the thyroid gland has been removed in order to decrease the work on the heart. The basal metabolic test gives exact information on the change in metabolism and the decrease in cardiac work following such an operation.

CHAPTER L

THE METABOLISM OF CARBOHYDRATES

Carbohydrate is the chief fuel of the body, for more than two-thirds of the required energy is supplied by its oxidation. In addition it enters into the composition of many substances, such as nucleic acids and cerebrosides, which form part of the basic tissue framework. The regulation of its storage and metabolism is more clearly understood than is that of protein or of fat. Knowledge of this control has been gained mainly from the study of diabetes as it occurs in man or as it is experimentally produced in animals. In this disease the abnormal carbohydrate content of the blood and urine may be analyzed by accurate chemical determination and controlled by insulin injections.

The Absorption of Carbohydrates.—The carbohydrates of the food are of three general types: polysaccharides which may be hydrolyzed into monosaccharides by the action of the digestive enzymes; polysaccharides which resist hydrolysis; and monosaccharides. The nonhydrolyzable polysaccharides are excreted in the feces while the other polysaccharides are broken down into their constituent monosaccharides and are absorbed along with the monosaccharides occurring in the food. Cori[119] has demonstrated a differential rate of absorption for the hexoses. He found that galactose is absorbed faster than glucose which, in turn, is taken up by the blood at a faster rate than fructose or mannose. The rate of absorption depends on the chemical structure of the sugar and not on the absolute amount of sugar present in the intestinal tract. In the normal animal the latter factor affects only the duration of absorption. For a more detailed discussion of this subject see Chapter LXVIII.

Blood Sugar.—Following the ingestion of carbohydrate, there is an increase in the blood sugar. The normal level varies between 70 and 120 mg. per 100 ml. of blood.

The amount of sugar in the blood is determined by measuring the reducing power of a sample after removing the proteins. Numerous micromethods have been developed for this purpose. Since these methods determine the total reducing substances present in the sample of blood, none is specific for glucose. Glucose does, however, make up the greater part of the total reducing material; the remainder is composed of such substances as creatinine, thioneine and glutathione. The method that gives the closest approximation to the true glucose concentration involves a combination of reduction and fermentation. In this procedure the reducing power of the solution is determined before and after yeast fermentation. Assuming that the yeast reacts only with glucose, the difference between these two values gives the true glucose content. For most clinical purposes, however, the reduction alone yields results of sufficient accuracy. Different sugars have various powers of reduction. Hawkins[143] has shown that if a given weight of glucose be taken as a standard and given a reducing value of 1.00; equal weights of the other sugars have the following reducing powers: mannose 1.02; galactose 0.79; fructose 0.99; arabinose 0.95; xylose 1.02; maltose 0.73; and lactose 0.73. These ratios as well as the normal basal values of the blood sugar vary slightly with the method used. Van Slyke and Hawkins[192] have compared the values obtained for the blood sugar level when different methods are used. It is interesting to note the different results obtained from the same blood with the different methods (Fig. 285).

After removal of blood from the body its sugar content may decrease even when it is kept under sterile conditions. Evans[128] has shown that the disappearance of sugar under these conditions is accounted for by the appearance of lactic acid. It is necessary, therefore, to analyze blood immediately after withdrawal from the body or to inhibit the glycolysis by the addition of fluoride.

Glucose Tolerance Test.—The blood sugar changes that occur after the ingestion of glucose have been incorporated in a test for the capacity of the body to absorb and to utilize carbohydrate. The main essentials of this test consist in giving 50 to 100 grams of glucose by mouth and then determining the concentration of sugar in the capillary blood at fifteen-minute intervals

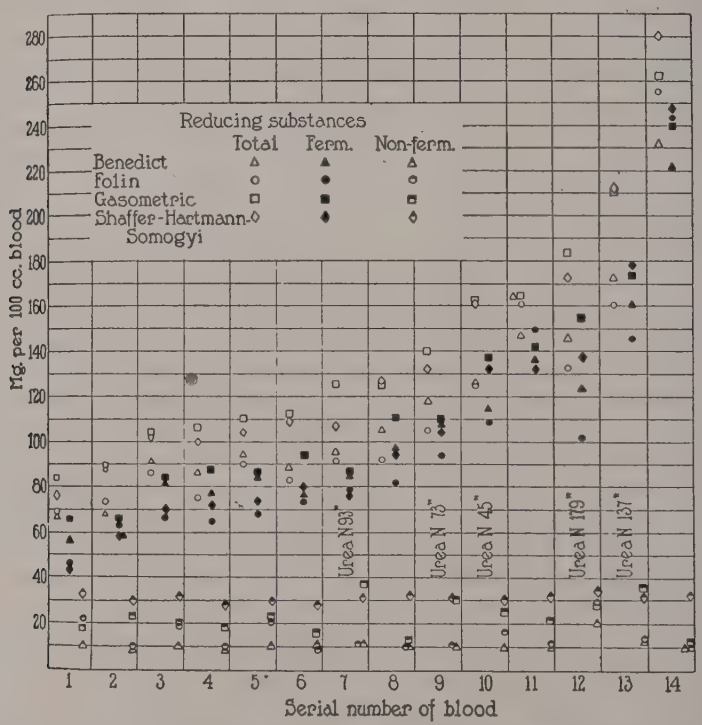


Fig. 285.—Values of normal blood sugar analyses obtained by different methods. (From Van Slyke and Hawkins: J. Biol. Chem. 83: 51, 1929.)

for several hours. Gilbert, Schneider and Boek[147] determined the variation in the course of the sugar curves in a group of individuals each of whom received in 400 ml. of water 1.75 grams of glucose per kilogram of body weight. They found that the maximum rise is reached in from fifteen to forty-nine minutes and that the maximal concentration varies from 136 to 206 mg. per 100 ml. of blood. The return to normal was found to take place in two and a half hours. In some individuals a secondary rise occurred. The rise in blood sugar is not directly proportional to the amount of glucose taken; large doses merely prolong the hyperglycemia and require more determinations in order to

obtain the complete curve. Peters and Van Slyke[167] recommend 1 gram of glucose per kilogram of body weight as the optimal amount to be given in carrying out a tolerance test.

In the individual suffering from diabetes mellitus an entirely different curve is obtained after ingestion of glucose. The maximal rise is greater, reaching values as high as 300 mg. per 100 ml. of blood, and the return to the base line is delayed (Fig. 286). The maximal rise, in contrast to the response of a normal subject, is proportional to the amount of sugar ingested. This test, therefore, is of special value in the diagnosis of diabetes. A normal response in an individual is fairly good evidence that the subject is not suffering from this disorder. An abnormal response, although it may be the result of other pathological conditions, must be looked upon with suspicion even if the level of the postabsorptive blood sugar is within normal limits. The earliest sign of diabetes is an unusual degree and duration of the postprandial hyperglycemia. In the diagnosis of diabetes the duration is of more importance than the degree of the hyperglycemia.

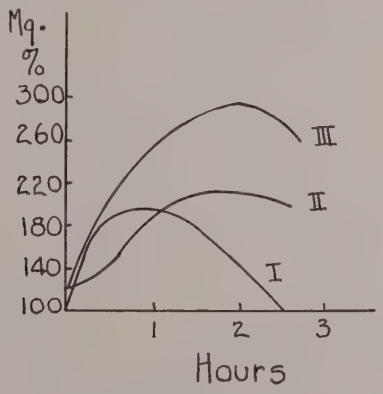


Fig. 286.—Capillary blood sugar curves (compiled from various sources). I, maximal normal rise after ingestion of 1 gram of glucose per kilogram of body weight; II and III, rises in a diabetic subject after ingestion of 35 and 58 grams of glucose, respectively.

Numerous modifications of this test have been suggested. Traugott,[191] Exton and Rose[129] and others have proposed a two-dose test, in which the second ingestion of glucose is given about one hour after the first. These tests are based on the fact that the more glucose that is given to a normal individual, the more the normal individual will use, whereas this is not the case in the diabetic. The authors of these tests claim that they are more specific for the diagnosis of the diabetic condition than the usual one-ingestion test.

Fate of Ingested Carbohydrate.—The glucose tolerance tests demonstrate that in a normal person the blood sugar returns to a normal value within a period of from two to two and a half hours after the ingestion of 100 grams of glucose. The processes which may be involved in the disappearance of the sugar from the blood are the following:

1. *Removal From Blood Stream by Diffusion.*—Some of the glucose passes directly into the tissues following the increased concentration in the blood.

Folin, Trimble, and Newman[132] observed that the percentage of sugar in the skin varies with the amount in the blood. No chemical change in the sugar molecule takes place in this process and the concentration in the tissues follows the level in the blood. Cori, Closs and Cori[122] have shown that the fermentable sugar in skeletal muscles of rats amounts to 10 to 12 mg. per cent at plasma sugar levels of 80 to 120 mg. per cent. At the same blood plasma level heart muscle has a higher concentration of glucose than skeletal muscle. Cannon[117] has called the process of diffusion of sugar into the tissues "storage by inundation."

2. *Conversion of Glucose to Glycogen.*—In contrast to the simple overflow of carbohydrate into the tissues there is another form of storage in which the glucose is changed chemically to glycogen. Cannon[117] describes this process as "storage by segregation." In contrast to the large amounts of glycogen found in the liver, muscles, and other tissues, the amount of carbohydrate present in the body as glucose is very small. Cori[120] has determined the rate of glycogen formation in the livers of rats following the ingestion of various sugars. Fructose and glucose form glycogen at equal rates, whereas galactose does not form glycogen readily. Glycogen formation reaches a maximum after four hours of absorption of fructose and glucose. In Cori's experiments, the liver was able to store only 17 per cent of the absorbed glucose and 39 per cent of the fructose.

The liver is essential not only for storage of sugars but also for the transformations which sugars or sugar-producing substances undergo in order that they may be utilized by the body. Mann[162] found that glucose or fructose can be used for the maintenance of the blood sugar level in an animal from which the liver has been removed. Other substances, such as glycine and lactic acid, cannot be used by these animals and, therefore, it may be concluded that they must undergo a preliminary transformation in the liver before they can be used in the animal body. The glucose circulating in the blood may be built into glycogen in muscles and other tissues as well as in the liver. Cori and Cori[120] observed that of ingested glucose 18 per cent is deposited as liver glycogen while 25 per cent is found as glycogen in other tissues of the body.

3. *Oxidation of Glucose.*—In this same work, Cori and Cori determined the amount of glucose oxidized by rats during the four hours following glucose ingestion. Nearly all the sugar was accounted for by the two mechanisms: glycogen formation and carbohydrate oxidation. In contrast to our knowledge of the intermediate steps in the breakdown of glycogen very little is known about the direct utilization of glucose by tissues. The increased oxidation of carbohydrate following absorption of glucose may be due to the combustion of the glycogen formed from the glucose and not to the oxidation of glucose itself. Evidence has been presented that the brain and heart are able to use glucose directly. Ashford and Holmes[102] have shown that glucose may be converted to lactic acid by chopped brain tissue. Gaddie and Stewart[133] have investigated the action of glucose and mannose on the fatigued heart. These substances serve to reduce fatigue developed under anaerobic conditions. Since the formation of glycogen from glucose requires energy which may be obtained from oxidative processes, these experiments suggest that the glucose may be used directly for the production of energy. Although glucose may be oxidized to a limited extent, the conversion of glucose to glycogen and the oxidation of the glycogen is of greater importance in the carbohydrate cycle.

4. *Removal by Kidneys.*—There is a limit to the amount of carbohydrate that an animal is able to absorb without the occurrence of sugar in the urine. The total amount which may be tolerated without glycosuria is called the *assimilation limit.* This varies with the type of sugar ingested and with the rate at which the tissues are able to take sugar from the blood. In order to determine the latter factor, Woodyatt, Sansum and Wilder[198] developed a method for continuous injection of sugar solutions into man and animals. They found that a man weighing 70 kilograms was able to absorb 63 grams of glucose per hour by vein without exhibiting glycosuria. The average normal tolerances for various sugars are given in Table XLVII.

TABLE XLVII

NORMAL TOLERANCES FOR VARIOUS SUGARS INJECTED INTO A VEIN (WOODYATT, SANSUM AND WILDER[198])

SUGAR	TOLERANCE (GRAMS PER KILOGRAM BODY WEIGHT PER HOUR)
Glucose	0.85
Fructose	0.15
Galactose	0.10
Lactose	0.00

The limit of assimilation of glucose following ingestion of sugar by mouth is much greater than the values given above for injected sugars. Taylor and Hulton[190] fed varying amounts of sugar to a group of subjects and found that some individuals were able to tolerate as much as 400 grams of glucose without showing glycosuria. The reason that man is able to withstand such large amounts of ingested sugar is that the maximal rate of absorption from the intestine is less than 1 gram per kilogram of body weight per hour. This is a limit which lies just within the tolerance found by Woodyatt and his associates for the slow intravenous injection of glucose. These findings explain why the tolerance of man to the carbohydrate in his food is practically without limit. There are some individuals, however, who do develop *alimentary glycosuria.* In these, the glycosuria may not develop until after the peak of the blood sugar curve has been reached, and then the kidneys may continue to pass glucose even when the blood sugar has fallen to the normal level. Therefore, there are two thresholds for glucose, one for the ascending blood sugar and one for the descending, the latter threshold being lower than the former.

5. *Conversion of Carbohydrate to Fat.*—It is assumed that carbohydrate may be converted into fat. The only experimental evidence for this conversion

TABLE XLVIII

THE MAXIMUM CONVERSION OF CARBOHYDRATE TO FAT (FROM RAPPORT[169])

OBSERVER	ANIMAL	FAT DEPOSITED IN 24 HOURS	
		AMOUNT (GRAMS)	PER CENT OF BODY FAT
Munk (1885)	Dog	37	0.1
Rubner (1886)	Dog	20	0.3
Lehmann and Voit (1901)	Goose	18	0.4
Bleibtreu (1901)	Goose	104	2.2
Meissl (1886)	Pig	364	0.2
Rapport, Weiss and Csonka (1924)	Pig	82	0.3
Baumgardt and Steuber (1920)	Man	148	0.25

has been obtained during the feeding of excessive amounts of sugar (Table XLVIII). Whether this conversion occurs during the ingestion of normal amounts of carbohydrate has not been determined experimentally nor has the exact chemical nature of the conversion been demonstrated. Leathes and Raper[152] have suggested that aldehydes condense to form long chain unsaturated compounds which in turn are oxidized to fatty acids:

$$4CH_3CHO \rightarrow CH_3(CH)_6CHO \rightarrow CH_3(CH_2)_6COOH$$

Smedley and Lubrzynska[182] have postulated another pathway, one in which pyruvic acid combines with an aldehyde to form a keto-acid; the latter is then oxidized to the corresponding fatty acid.

Noncarbohydrate Sources.—Carbohydrates may be formed from other foodstuffs. Experimental evidence for the change of protein into carbohydrate has been obtained by several methods. Williams, Riche and Lusk[195] studied the output of nitrogen and carbon following the feeding of 1200 grams of meat to a dog. They found that the respiratory carbon dioxide was less than the theoretical amount calculated on the basis of complete protein oxidation. The remainder of the carbon evidently had been stored either in the form of fat or carbohydrate or both. More direct evidence of the transformation of protein to carbohydrate has been obtained in the diabetic animal. Reilly, Nolan and Lusk[170] fed a phlorhizinized dog 500 grams of meat and found that the urinary output of glucose and nitrogen doubled. From these results, they calculated that 58.7 per cent of meat protein may be converted into sugar. Comparable results have been obtained in pancreatectomized animals and in persons suffering from diabetes. Not all the amino acids give rise to extra sugar in the diabetic animal. Dakin[124] found that glycine, alanine, serine, cysteine, proline, ornithine, and arginine are converted into glucose while valine, leucine, isoleucine, lysine, histidine, phenylalanine, and tryptophan give little or no sugar. Such experiments may be criticized on the ground that since they were carried out in the diabetic animal the results may not apply to the normal. Evidence, however, has been obtained by feeding normal animals protein and amino acids after most of the supply of carbohydrate had been removed by starvation, muscular exercise, exposure to cold, or by administration of strychnine. After diminishing the glycogen stores in rats Wilson and Lewis[196] found that alanine, casein, or gelatin may increase the amount of glycogen in the bodies of these animals. More recently, Butts, Dunn and Hallman[116] have shown that dl-phenylalanine causes a deposition of glycogen when fed to fasting rats.

Another possible source of carbohydrate is fat. The evidence for this transformation, however, is not as definite as that for the conversion of protein into carbohydrate. Soskin[183] fed fat and lecithin to diabetic dogs. In three out of fifteen experiments he observed an increase of sugar in the urine. In numerous experiments fat has been fed animals after a period of starvation. The small changes observed in the sugar content of these animals may be accounted for by the transfer of the glycerol in the neutral fat to glycogen. Gemmill and Holmes[135] found low respiratory quotients (0.41-0.72) and definite increments in the carbohydrate content of livers taken from rats on a butter diet. Weil[194] has demonstrated that acetoacetic acid is converted into carbohydrate in kidney slices. Blixenkrone-Møller[108] has shown that a change of butyrate to carbohydrate can take place in the perfused liver. Although the

amount of carbohydrate coming from fat may be small, the possibility of its conversion must be considered in any metabolic process.

Many non-nitrogenous substances, such as glycollic aldehyde ($CH_2OH.CHO$), lactic acid ($CH_3CHOHCOOH$), and glycerol ($CH_2OHCHOHCH_2OH$) are convertible to glucose.

The Specific Dynamic Action of Glucose.—Following the ingestion of sugar there is an increase in metabolism. The rise in metabolism is related to the existing glycogen stores in the body. Dann and Chambers[125] found that glucose fed a fasting animal produces a greater rise in metabolism than when the same amount of glucose is fed an animal on a normal diet. This change in the metabolism may take place in the muscles, for removal of the liver does not abolish the rise; it may be associated with the production of glycogen from glucose.

The Fate of Glycogen.—If liver tissue containing glycogen is removed from an animal, the glycogen content decreases while the concentration of glucose increases. The enzyme responsible for the breakdown of glycogen into glucose is called glycogenase. Macleod[157] studied the distribution of this enzyme in various tissues by determining the extent of glycogenolysis. His results are given in Table XLIX.

TABLE XLIX

DISTRIBUTION OF GLYCOGENASE (MACLEOD[157])

ORGAN	PER CENT GLYCOGENOLYSIS IN 4 HOURS
Pancreas	100.0
Liver	88.6
Serum	83.3
Kidney	48.9
Muscle	0.0

It is interesting to note that the pancreas contains the greatest amount of this enzyme. There must be some mechanism or arrangement in the tissues whereby this enzyme is separated from the glycogen; if this were not the case the organs would not be able to store glycogen.

Although withdrawal of food reduces the glycogen content, small amounts may be found even after long periods of starvation. It has long been recognized that vigorous exercise (Külz[150]) and exposure to cold (Külz[151]) are effective means of depleting the store of liver glycogen. The glucose formed under these conditions is transported to the tissues where it is used as fuel. The various factors which cause considerable changes in liver glycogen do not affect muscle glycogen to the same degree. For example, starvation of two or three days' duration may cause nearly all the liver glycogen to disappear without producing any marked changes in muscle glycogen. Severe exercise, however, will reduce muscle glycogen. The chief intermediate product of glycogen breakdown in the muscles is lactic acid, not glucose. The breakdown of glycogen to lactic acid is discussed in the chapter on the Chemistry of Muscular Contraction (Chapter LII).

CHAPTER LI

THE CONTROL OF CARBOHYDRATE METABOLISM

The level at which the concentration of the sugar in the blood is maintained represents a balance of the numerous factors discussed in the previous chapter. The two main elements are the utilization of glucose by the tissues and its liberation from the liver. Since the need for sugar by the tissues is a variable one, mechanisms exist whereby the production of sugar in the liver may meet the demand for glucose.

NERVOUS AND NEUROHUMORAL CONTROL OF CARBOHYDRATE METABOLISM

Pontile Injury.—The first evidence that the blood sugar level is under the control of the central nervous system was obtained by Claude Bernard. In the course of his investigations on glycogen (1849-1877) Bernard[107] discovered that puncture (piqûre) of the floor of the fourth ventricle causes a transitory outpouring of sugar in the urine, an event which he recognized as the consequence of a rise in blood sugar. He concluded that a center in the region of the pons controls

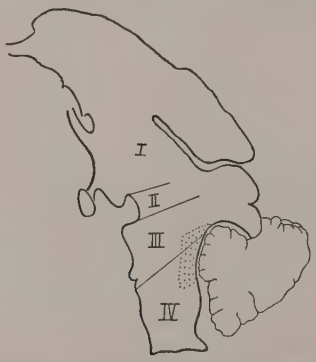


Fig. 287.—Diagram indicating the regions of the rabbit's brain through which experimental transections were made in the experiments of Donhoffer and Macleod. (From Macleod: Bull. Johns Hopkins Hosp. 54: 79, 1934.)

the blood sugar level and that the glucose mobilization in his experiments was due to irritation of this center. Since Bernard's time much work has been done on puncture glycosuria and hyperglycemia. While it is true that almost any injury of the central nervous system may cause a transitory rise in blood sugar, the somewhat more pronounced effects of a puncture of the floor of the fourth ventricle denote the presence there of some central mechanism which is in specific control of carbohydrate metabolism. Donhoffer and Macleod[127] investigated this problem by studying the effects of lesions and transections in various parts of the brain stem. For purposes of consideration they have divided the brain into four regions: Region I is rostral to the aqueduct of Sylvius; Region

II lies between I and the pons; Regions III and IV are, respectively, the pontile and distal portions of the medulla oblongata (Fig. 287). The results obtained on decerebration at these different levels are given in Table L.

TABLE L

BLOOD SUGAR AFTER TRANSECTION OF THE BRAIN STEM AT VARIOUS LEVELS (MACLEOD[99])

LEVEL OF DECEREBRATION	BLOOD SUGAR (GRAMS PER 100 ML.)						NUMBER OF EXPERIMENTS
	BEFORE	IMMEDIATELY AFTER	1 HR. AFTER	2 HR. AFTER	3 HR. AFTER	4 HR. AFTER	
I	0.102	0.127	0.139	0.145	0.155	0.174	10
II	0.123	0.125	0.125	0.139	0.130	0.160	6
III	0.110	0.155	0.195	0.241	0.286	0.291	23
IV	0.109	0.137	0.123	0.135	0.131	0.126	10

In all these experiments a steady rise in blood sugar was obtained, but it was much more pronounced when the cut was made through Region III. Similar results were obtained by Bell, Horne, and Magee[105] who decerebrated rats which had been on high carbohydrate diets.

The question arises as to the nervous pathways involved in the blood sugar changes which follow central excitation. Macleod[99] reported that the effect is abolished by cutting the splanchnic nerves. Therefore the impulses concerned either pass through the splanchnics directly to the liver or proceed over the splanchnic (preganglionic sympathetic) fibers which innervate the adrenal medulla and are capable of causing liberation of adrenine into the blood stream. It is well known that this internal secretion acts to produce a rise in blood sugar. Section of the splanchnics denervates both the liver and the adrenals and cannot therefore be used to determine which of these glands is acted upon as a result of the nervous discharge. Macleod[99] found, however, that removal of the adrenal glands without interruption of the splanchnic pathway to the liver abolishes the rise in blood sugar produced by decerebration. Previous to Macleod's work a number of investigators had found that activation of the adrenal medulla is the essential factor involved in various neurogenic hyperglycemias. Britton,[112] for example, had demonstrated the prepotency of adrenal secretion in the production of the hyperglycemia which accompanies strong emotional excitement. He showed that after removal of the medulla of both adrenal glands excitement in cats fails to raise the glycemic percentage. On the other hand, section of the sympathetic nerves to the liver scarcely modified the response.

The more recent work of Noltie[166] has confirmed and extended the findings of Macleod. This author found that midbrain or pontil decerebration evoked a marked rise in blood sugar that persisted for three to four hours. These changes did not occur if the adrenal glands were removed prior to the pontine section. From these experiments there can be no doubt that transection of the pons produces an increase in the blood sugar through liberation of adrenine from the medullas of the adrenal glands.

An influence on blood sugar may be exerted through the parasympathetic system. Following experimental exclusion of the sympatho-adrenal factor, Britton[112] obtained a lowering of the blood sugar as a result of stimulation of the peripheral end of the cut vagus nerve. Macleod[99] observed that section of the vagi or the administration of atropine abolishes the

rise which follows pontile lesions in the fasting rabbit. In rabbits with high liver glycogen the usual rise was obtained under similar experimental conditions. It is obvious that more work is needed in this field before all the pathways for the nervous control of carbohydrate metabolism can be defined with assurance.

Reflex Effects.—Additional evidence for the nervous control of carbohydrate metabolism has been secured in studies of the blood sugar changes which are produced by stimulation of afferent nerves. Griffith,[139] using rabbits, found a prompt increase in blood sugar on stimulating the central end of the cut crural or sciatic nerve. After bilateral adrenalectomy the magnitude of this reflex hyperglycemia was decreased. Stimulation of the central end of the cut vagus also increased the concentration of sugar in the blood and this change was not diminished by removal of the adrenals. Brooks[115] studied the location of the central mechanism essential for reflex hyperglycemia by testing this response in cats which had been subjected to transections of the brain stem at various levels. His results show that this reflex "center" is situated in the floor of the fourth ventricle caudal to the middle of the brachium pontis. Doubtless it is this mechanism which is thrown into action by Bernard's puncture or such transections and lesions as those practiced by Donhoffer and Macleod.

Epinephrine.—Since the adrenals play such an important part in the rise of blood sugar following reflex, emotional or direct stimulation of the central nervous system, another approach to this problem has been through a study of the changes in carbohydrate metabolism which are induced by injections of epinephrine. Experiments of this nature have been carried out, particularly by Cori and Cori.[123] Their findings are summarized in Table LI, which shows that, after injection of epinephrine, there is a decreased deposition of glycogen

TABLE LI

CARBOHYDRATE METABOLISM FOLLOWING THE SUBCUTANEOUS INJECTION OF EPINEPHRINE (0.02 MG. PER 100 GM. BODY WEIGHT IN 0.1 ML. OF FLUID) (CORI AND CORI[123])

	CHANGES PER 100 PARTS OF ABSORBED SUGAR				
	OXIDIZED	DEPOSITED AS LIVER GLYCOGEN	DEPOSITED AS GLYCOGEN IN THE REST OF THE BODY	RETAINED IN BODY FLUIDS	EXCRETED IN URINE
Controls	44	18	25	2	0
Epinephrine	39	23	15	5	6
Differences	–5	+5	–10	+3	+6

in tissues other than the liver, a decreased oxidation of sugar by the body, and an increase in the liver glycogen. In other experiments Cori and Cori determined the concentrations of glucose and lactic acid in the blood after epinephrine injections. From the results of these two types of experiments they concluded that epinephrine causes an increased mobilization of sugar from muscles and liver. The muscle glycogen forms lactic acid which is carried to the liver and is there converted into glucose which is transported to the muscles.

The total change in the blood sugar is greater than can be accounted for by the small changes in the glycogen content in the tissues (Macleod[158]). Therefore, several additional factors may be operating. There may be a decrease in utilization of sugar in the muscles or an increase in liberation of glucose from noncarbohydrate sources in the liver. Direct observation (Soskin[187])

has not demonstrated any decrease in utilization of glucose by the muscles; therefore, there must be augmented production of carbohydrate from noncarbohydrate sources in the liver. Experiments have not, however, been made to test that assumption. Regardless of the actual mechanisms involved in the production of hyperglycemia by epinephrine, the evidence is clear that the sympatho-adrenal mechanism plays a very important part in the maintenance of normal blood sugar levels.

The Hypothalamus.—In addition to the blood sugar changes observed by lesions in the pons, numerous investigators have described changes resulting from lesions or stimulation of the hypothalamus. Barris and Ingram[105] produced localized lesions in the hypothalamus in 55 cats. In 42 of these animals, a transient postoperative hyperglycemia was observed. Ten of this group showed a mild chronic hypoglycemia which was frequently intermittent. In a later review Ingram[148] described these effects as probably due to irritation resulting from the lesion. Direct stimulation of this region will also affect the blood sugar level (Magoun, Barris and Ranson[159]). Magoun, Ranson and Hetherington[160] have shown that adrenine and sympathin are liberated by continuous stimulation of the hypothalamus. The mechanism for the production of the hyperglycemia may be through the sympatho-adrenal mechanism (see page 168), since adrenine is well known to be a hyperglycemic agent (see below) and since sympathin liberated by stimulation of the cardio-accelerator nerves has been demonstrated by Bodo and Benaglia[110] to cause hyperglycemia.

THE HUMORAL CONTROL OF CARBOHYDRATE METABOLISM

The Relation of the Pancreatic Islet Tissue to Carbohydrate Metabolism

Pancreatic Diabetes.—In 1889 von Mering and Minkowski[164] observed, in dogs from which they had removed the pancreas, a persistent glycosuria accompanied by other symptoms of the disease, diabetes mellitus. The animals showed marked hunger and thirst, emaciation in spite of liberal feeding, and they died in the course of three weeks, or less. These authors reported that the extirpation must be complete to obtain this result; a small remnant of the gland sufficed to keep the animals in good health. These classical experiments demonstrated that the pancreas exerts an influence of the first importance on carbohydrate metabolism, and they led the way to the discovery of one of the most essential hormones, *insulin*.

Although von Mering and Minkowski attributed the condition of their pancreatectomized dogs to the elimination of an internal secretion of the pancreas, it was not until later that this was proved beyond any vestige of doubt. At the time of their work it was conceivable that pancreatectomy exerts its influence on carbohydrate metabolism by eliminating the *external* secretion which has its origin in the acinar tissue of the gland and is conveyed to the duodenum. In 1869 Langerhans described the pancreatic islet tissue which bears his name and which soon came to be regarded as the source of an *internal* secretion. Toward the end of the decade which followed von Mering and Minkowski's discovery a number of investigators showed that ligation of the pancreatic ducts, although followed by degeneration of the acinous tissue with scarcely any change in the islets, does not produce any of the symptoms of diabetes. Long before the preparation of an active extract capable of relieving the diabetic symptoms it was so fully established that a hormone is produced by the islet tissue that Schäfer (in 1916) gave it the name insulin. Two lines of evidence which pointed to its existence may be mentioned. (1) In 1908 Minkowski succeeded in grafting a piece of pancreas subcutaneously in a dog and found that subsequent removal of the animal's pancreas failed to induce diabetes.

(2) Later Hédon (1913) showed that transfusion of blood by anastomosis from the pancreatic vein of a normal dog to the jugular vein of a diabetic dog greatly ameliorated the symptoms of the recipient.

The course of the diabetes produced by complete pancreatectomy is more severe than that usually observed in man, and it is extremely acute from the start. Experimental diabetes very closely simulating the disease in man can be induced by excision of the greater part of the pancreas after which the animals for some months only occasionally show glycosuria, if at all. This symptom, however, becomes more and more frequent, until at last the condition typical of complete pancreatectomy supervenes. The main features of the disorder are discussed in the following paragraphs.

Glycogen.—The first change that occurs after removal of the pancreas is a disappearance of glycogen from the liver. Minkowski[165] observed that only traces of glycogen are found in the livers of pancreatectomized dogs and that feeding glucose to such animals does not restore the hepatic glycogen. These results have been confirmed by many workers. Fisher and Lackey,[130] for example, found that the liver glycogen of normal dogs fed meat for five days averaged 1.81 per cent while livers from diabetic animals on the same diet contained only 0.11 per cent glycogen; the liver glycogen of a diabetic dog fed glucose for thirteen days was only 0.045 per cent. After complete pancreatectomy the glycogen content of skeletal muscle does not change as rapidly as that of the liver. The same investigators observed that diabetic dogs on a diet of meat had a muscle glycogen content of 0.31 per cent whereas the skeletal muscles of normal control animals contained 0.58 per cent glycogen. The glycogen content of cardiac muscle actually increases, for these authors found an average value of 0.80 per cent for cardiac muscle from diabetic dogs and one of 0.50 per cent for the myocardium of normal animals. Although the values for the glycogen content of these organs vary greatly in a series of individual experiments, they do show the general trend of the changes that take place after removal of the pancreas.

The fact that the glycogen does not entirely disappear from the liver and muscle shows that these organs do not completely lose their ability to store this food material. Major and Mann[161] found that a diabetic animal could store glycogen in its liver and muscles if glucose was given, but not to the same extent as the normal animal. Barker and Sweet[104] have also shown that considerable storage occurs in the muscles if high concentrations of blood glucose are maintained. Reformation of glycogen occurs in the muscles of a diabetic animal after muscular contraction although the velocity of this process is impaired (Lukens[155]). Bodo and his associates[109] have demonstrated also that glycogen can be stored to a limited degree in the liver of a diabetic animal.

Blood Sugar.—With the decrease of glycogen in the liver and skeletal musculature, there is an increase in the blood sugar. Mann and Magath[163] have demonstrated that the liver is necessary for this hyperglycemia. After removal of its liver a diabetic dog shows hypoglycemia. The muscles may contribute indirectly to the blood sugar by the breakdown of muscle glycogen into lactic acid with the subsequent conversion of the lactic acid into glucose in the liver. Weber, Briggs and Doisy[193] have shown that diabetic muscles retain their power of forming lactic acid during muscular contraction.

Glycosuria.—Because of the rise in blood sugar in the diabetic animal there is marked glycosuria. Sugar continues to be excreted by the animal during starvation. Chambers and Coryllos[118] followed the changes in blood sugar, urinary sugar, and urinary nitrogen in successive three-hour periods after pancreatectomy. Immediately after the operation there was a rise in blood sugar and urinary nitrogen. Glucose did not appear in the urine until the blood sugar reached a level of about 0.180 per cent. They concluded that part of the early increase in the nitrogen excretion was due to tissue trauma during the operation, while the marked increase that occurred later was the result of increased protein catabolism. With the loss of glucose from the body a greater demand is made on protein metabolism for energy and for glucose.

Glucose : Nitrogen Ratio.—Many attempts have been made to relate the output of glucose in the starving diabetic animal to protein metabolism and especially to determine whether protein from the body tissues is the source of the sugar which continues to be excreted after all stores of carbohydrate have been exhausted. Theoretically it is possible to calculate, on the basis of observations made on the ability of amino acids to form sugar that 100 grams of meat protein may yield 44 grams of sugar in the animal body. Since 100 grams of protein contain, on the average, 16.65 grams of nitrogen, the ratio, $\frac{\text{grams of glucose excreted}}{\text{grams of nitrogen excreted}}$ would be constant at about 2.7 in a diabetic animal, if all the sugar were derived from protein. This ratio is called the glucose : nitrogen or G : N ratio (also the dextrose : nitrogen or D : N ratio). In experimental diabetes produced by pancreatectomy ratios approaching 2.7 are obtained only in rare cases. For example, in a series of dogs kept in good condition after removal of the pancreas, Macleod[157] found ratios which varied from 0.91 to 11.3. Doubtless the figure is influenced by the amount of glycogen stored in the liver. Closer approximations to the theoretical value of 2.7 have been obtained in diabetic animals kept on a meat diet. Minkowski[163] found ratios of from 2.63 to 3.05, averaging 2.8, under these conditions. In view of the large variations in the value of this ratio which are encountered experimentally in the starving diabetic animal, too much emphasis should not be placed on it as an index of the amount of glucose derived from protein.

Macleod critically examined the question whether the G:N ratios of diabetic animals in varying states of bodily nutrition are such as to support the widely accepted view that protein is the sole source of glucose after all available stores of carbohydrate have been used up. As indicated above, the G:N ratio does not have the constant value which in all strictness that view demands. In fact, Macleod found that after withdrawal of insulin and food the majority of diabetic dogs have ratios which are considerably in excess of 2.7. He concluded that under these circumstances sugar is being derived from other sources than protein. His interpretation of the matter was that fat represents the chief nonprotein source of carbohydrate.

Respiratory Quotient.—With the loss of carbohydrate from the body there is a fall in the respiratory quotient. Ralli, Canzarelli and Rapport[168] determined this quotient in a series of diabetic dogs before and after the ingestion of meat. They found that under basal conditions the quotient averaged 0.71 and after feeding meat it rose to an average value of 0.72. They calculated that the theoretical respiratory quotient of meat protein in the diabetic animal body should be 0.73; they deducted the amount of carbon, hydrogen, and oxygen that

would be lost by conversion to sugar. Therefore the low quotients observed in the diabetic animal may signify a combustion of protein, as such, or fat or a mixture of these two substances.

Acetone Bodies.—Acetone, acetoacetic, and β-hydroxybutyric acids are found in large amounts in the blood and urine of diabetic animals. These substances are formed during the incomplete oxidation of fats and they occur in the blood and urine of otherwise normal men and animals when the supply of carbohydrate is decreased or the oxidation of carbohydrate blocked. The mechanism of their formation will be discussed in the chapter on the Metabolism of Fat.

The formation of these nonvolatile acids disturbs the acid-base balance of the blood, since a certain amount of base must be matched against these acid ions. This reduces the available base for the carrying of the bicarbonate ions and thus there is a reduction of the carbon dioxide combining power and a decrease in the pH of the blood in the diabetic.

Polyuria.—With the loss of sugar and acetone bodies in the urine, there is an increase in the amount of water lost from the body. The loss of acetoacetic acid and β-hydroxybutyric acid removes base from the body, thus causing a removal of water from the body. However, the loss of sugar itself produces a loss of water, since a glycosuria unaccompanied by ketonuria causes an increased urinary volume (Himwich and Fazekas[144]).

Insulin.—The question arises now as to the explanation of the extra glucose appearing in the blood and urine of the diabetic animal. Two general theories have been offered: either there is a lack of oxidation of carbohydrate or there is an overproduction of sugar from protein and fat. In either case it is certain that the distribution is the result of the absence or insufficiency of an internal secretion of the pancreas.

Since the demonstration by von Mering and Minkowski[164] that the pancreas is responsible for the production of diabetes in animals, many attempts have been made to obtain an active extract from this organ. The first potent preparation was made by Banting and Best.[103] It occurred to Banting that the enzymes in the acini of the pancreas might be antagonistic to the internal secretion of the gland, and that one should, therefore, remove the acini before attempting to make an extract of the islet tissue. This was done by ligating the pancreatic duct, a procedure which causes the destruction of the acini. After acinar degeneration, an active extract was prepared that produced in depancreatized diabetic dogs a sudden fall in the blood sugar and a marked decrease in the sugar content of the urine. These experiments proved conclusively that the islet tissue of the pancreas secretes a hormone, insulin, that regulates carbohydrate metabolism. Additional evidence was obtained by making extracts from the islet tissue of certain fish, Lophius, for example, in which the islet tissue forms a separate organ. Removal of this organ causes a marked rise in the blood sugar which may be brought back to the normal level by injection of extracts made from the islet tissue.

Abel and his co-workers[100] have isolated a crystalline compound from highly purified commercial preparations of insulin. Harington and Scott,[141] using a different method, have been able to obtain similar crystalline material. Scott[179] has shown that small amounts of zinc are necessary for the crystalline formation of insulin. Chemically, crystalline insulin shows the reactions of a typical protein and has been hydrolyzed to yield the following amino acids: cystine, tyrosine, glutamic acid, leucine, arginine, histidine, and lysine. The molecular weight

of the crystallized preparation averages 35,100 (Sjörgren and Svedberg[181]). Solutions of zinc insulinate are produced commercially. They give the same hypoglycemia in a normal animal (Sahyun[175]) as the amorphous type and are useful in cases showing reactions to the usual commercial preparations of insulin.

In order to standardize preparations of insulin, the Standardization Committee of the League of Nations (Gautier[134]) has defined a unit of insulin as having the specific activity contained in 0.045 mg. of the dry crystalline insulin hydrochloride. Thus 1 mg. of the crystalline material is equivalent to 22 international units. An unknown preparation may be tested against the standard by comparing its effect with the result obtained from the standard crystalline material.

Numerous attempts have been made to prolong the activity of insulin by combining the protein molecule with compounds that would decrease its rate of absorption from the tissues. The most successful of these experiments was that of Hagedorn and his associates[140] who showed that protamine in sodium phosphate buffer formed a complex with insulin. This complex had a prolonged hypoglycemic action. Scott and Fisher[180] demonstrated that a small amount of zinc added to the protamine insuline caused further prolongation of the activity. The practical importance of these findings is that patients need fewer injections of protamine zinc insulinate than of insulin, and that their blood sugar shows only minor changes during the intervals between injections.

Greeley[138] has estimated that insulin is needed at the rate of 0.0051 to 0.035 unit per kilo per hour. These are the rates at which insulin must be injected into a fasting depancreatized dog in order to keep the blood sugar at a normal constant level.

Action of Insulin in the Normal Animal.—When insulin is injected into a normal animal the blood sugar falls rapidly and may reach a point where characteristic symptoms appear. These hypoglycemic symptoms occur in rabbits when the blood sugar reaches a level around 0.045 per cent. In this animal the first symptom is a violent convulsion, during which the animal throws itself on the ground and rolls over and over. If the animal recovers from the original fit, a series of convulsions may follow until the animal dies of respiratory failure and reduced body temperature. A very quick recovery is obtained if the animal is given glucose. Other substances, such as mannose, fructose, lactic acid, and glycerol, may relieve the symptoms to a greater or less extent. In fact, such experiments may be used in determining whether or not a given substance is capable of forming glucose in the animal body. Cori[121] has determined the complete carbohydrate balance in fasted rats following injection of insulin (Table LII). These results demonstrate a decreased deposition of glycogen with an increased combustion of sugar after injection of insulin.

TABLE LII

CARBOHYDRATE BALANCE IN FASTED RATS AFTER INSULIN INJECTION (CORI[121])

	VALUES CALCULATED PER 100 GRAMS BODY WEIGHT						
	GLYCOGEN			TISSUE SUGAR	BLOOD SUGAR	NON PROTEIN R.Q.	CARBOHYDRATE OXIDIZED
	LIVER	REST OF BODY	TOTAL				
	MG.	MG.	MG.	MG.	MG. %		MG.
Fasted 24 hours	6	128	134	46	92	0.704	–
3 hours after Insulin	4	94	98	40	80	0.736	56
Differences	–2	–34	–36	–6			
Balance				–42			+56

The fact that the rise in the respiratory quotient is not accompanied by a large increase in oxygen consumption has led to the idea that insulin promotes an isocaloric shift in the metabolism. Instead of fats being consumed to supply

the basal energy, more carbohydrate is utilized under the action of insulin. Not all workers are in agreement that sugar is oxidized when insulin is injected into an animal. Bridge,[111] for example, has infused solutions of glucose with insulin into rabbits for periods of six hours. His results are given in Table LIII. These results show a shift from liver glycogen to muscle glycogen without a great loss in total carbohydrate.

TABLE LIII

RESULTS OF INFUSION OF GLUCOSE AND INSULIN INTO NORMAL RABBITS (BRIDGE[111])

INSULIN	GLUCOSE						
UNITS PER GRAM OF GLUCOSE GIVEN	INTAKE GRAMS	EXCRETED IN URINE GRAMS	RETENTION GRAMS PER KILO NET WEIGHT				
			TOTAL	LIVER GLYCOGEN	MUSCLE GLYCOGEN	BODY FLUIDS	OXIDIZED
—	22.6	1.35	10.8	3.8	2.3	2.0	2.8
1	21.8	0.80	11.2	1.9	4.0	1.2	3.9
4	23.7	2.30	10.7	0.8	5.2	2.2	2.7

Action of Insulin in the Diabetic Animal.—Quantitative data for the changes resulting in a diabetic man treated with insulin are given in Table LIV.

TABLE LIV

EFFECT OF INJECTION OF INSULIN INTO A DIABETIC PATIENT (LUSK[98])

TIME	R.Q.	URINE SUGAR GRAMS	BLOOD SUGAR %	CO_2 COMBINING POWER VOL. %	BLOOD ACETONE MG. IN 100 ML.
9:30	0.72	——	0.280	39.3	104
9:45	0.75	0.60	0.240	39.6	87
10:00	0.76	0.64	0.220	40.2	73
10:15	0.78	0.48	0.210	40.8	74
10:30	0.79	0.28	0.190	42.4	56
11:30	0.79	0.11	0.120	42.2	44
12:30	0.80	0.18	0.080	44.4	39

The fall in blood and urinary sugar, the rise in the R.Q. and the CO_2 combining power, and the changes in the blood acetone content on the administration of insulin are well illustrated in this table. In addition, insulin causes glycogen to be deposited in the liver and muscles of the diabetic, causes the body weight to increase, and prolongs life.

Nervous and Chemical Control of the Secretion of Insulin.—Very little is known about the mechanisms controlling insulin secretion. Britton[112] found that the blood sugar level of cats fell when the peripheral end of the cut right vagus was stimulated. This result suggests that the secretion of insulin is under nervous control. When the pancreas is transplanted to another position in the body, thus removing all nervous connections, the blood sugar remains at the normal level. While this experiment demonstrates that a nervous control is not necessary for the maintenance of the ordinary secretion of insulin, it does not by any means exclude the possibility of such a control.

It may be assumed that a rise in the blood sugar level increases the output of insulin. Such a response would explain the difference between the normal and the diabetic glucose tolerance curves. Recently Soskin and his co-workers[185] have shown that the pancreas is not essential for the production of typical glucose tolerance curves. In depancreatized animals, receiving sufficient insulin

to maintain a constant blood sugar level under basal conditions, normal glucose tolerance curves were obtained. Therefore, additional insulin is not necessary for the production of these normal curves. Evidence that blood sugar changes may affect insulin secretion by a direct action on the pancreas has been reported by Foglia and Fernandez who found that injection of hyperglycemic blood into a transplanted pancreas causes a fall in the sugar content of the systemic blood.

Mechanism of Insulin Action.—The physiological changes following the injection of insulin into normal and diabetic animals have been explained by two different theories. The first theory is that insulin promotes the storage and combustion of sugar. Therefore, in the diabetic, the ability to store and to oxidize sugar is lost and the loss of this function produces the hyperglycemia. The second theory is that insulin controls gluconeogenesis in the liver. If this control is lost, then overproduction of glucose results from the breakdown of protein and fat molecules. The evidence for the first theory is based: first, on the failure of the respiratory quotient to rise when glucose is ingested by the diabetic; second, on the recovery from the urine of most of the sugar which had been fed to the diabetic; and third, on the rise in the quotient following ingestion of sugar and the retention of the sugar when insulin is injected into the diabetic. The overproduction theory is based on the finding that the diabetic animal may oxidize sugar under some circumstances. Mann and Magath[163] showed that an animal without the pancreas or liver removes glucose from the blood stream. Diabetic animals use and oxidize carbohydrate after a period of starvation. This finding is called the Hédon phenomenon. Animals with both the pituitary and pancreas removed (Houssay animal) show positive tests for utilization of glucose. If the diabetic animal is able to use glucose, overproduction must take place to produce the high blood sugar. Young[199] has calculated from the data of several experimenters that the total amount of sugar produced by the liver in a normal fasting or diabetic dog could not come from the store of glycogen or from protein metabolism since the production was too great to be explained by the addition of these two processes. Consequently, the extra sugar must come from fat. Therefore, the overproduction theory must include the possibility of the transfer of fatty acids to glucose as well as the production of glucose from protein. The difficulty in deciding between these two theories lies in the lack of experimental proof for a large transfer of fat to carbohydrate and in the interpretation of data on the respiratory quotient.

The two theories may be combined in the following manner. The fact that storage of glycogen in muscles occurs in the diabetic, but only to a limited degree, suggests that this mechanism may be primarily affected when insulin is lacking. The lack of available glycogen in muscles may decrease secondarily the oxidation of carbohydrate. To meet this decreased storage, the body responds with overproduction of sugar in the liver, since increasing the blood glucose concentration aids in its storage and secondarily in its oxidation. When insulin is given, the rate of storage of glycogen in the muscles is accelerated, the blood sugar falls, and the need for overproduction is removed. This theory requires that insulin acts also as an inhibitor for overproduction in the liver. Normally, a high blood sugar will decrease the amount of sugar excreted by the liver, but in the diabetic, this mechanism seems to be lacking; hence an inhibitor is necessary.

Diabetes and Tissue Metabolism.—Howitt[147] has made the interesting calculation that 1 molecule of insulin may mobilize 700,000 molecules of glucose. The small amount of active material needed in this reaction points to an enzymatic process, controlled by the presence of insulin, which is inactive or only partially active in the diabetic state. Numerous attempts have been made to study diabetic tissue with modern techniques in the attempt to discover the actual site of the action of insulin.

Shorr, Richardson and Sweet[176] have determined the respiratory quotients of excised muscular tissue of diabetic dogs. They observed that the oxygen consumption of normal and diabetic excised muscle is the same whereas the R.Q. of the diabetic tissue was 0.73 in contrast to 0.94 in the normal. Shorr[177] has shown that the low R.Q. of diabetic tissue rises after several hours in the Warburg vessel. This corresponds to the Hédon phenomenon in animals. Shorr, Richardson and Sweet[176] have shown that tissue from a Houssay animal shows a normal R.Q., indicating some oxidation of carbohydrate. Krebs and Eggleton[149] have described an increase in oxygen consumption when a solution of insulin and citrate was added to pigeon's muscle. That this reaction is specific for pigeon's breast muscle was shown by Shorr and Barker[178] and Stadie, Zepp and Lukens[189] who repeated these experiments using a variety of other muscles and obtained negative results. Gemmill[136] has shown that insulin promotes glycogen storage in isolated muscle.

Other glands besides the pancreas play important roles in the maintenance of normal carbohydrate metabolism. These are the pituitary, adrenal, and thyroid glands.

The Relation of the Pituitary Gland to Carbohydrate Metabolism

Although well fed animals in which the pituitary gland has been removed show no apparent evidences of alteration in carbohydrate metabolism, there are deficiencies which may be elicited by injection of insulin or by removal of food. Only about one-tenth of the dose of insulin required to throw a normal animal into insulin convulsions is necessary to produce a similar response in an animal lacking the pituitary gland. The second factor, removal of food, soon lowers the blood sugar and throws the animal into a hypoglycemia crisis from which it may be rescued by the prompt injection of glucose. Both of these facts point to altered control of carbohydrate metabolism, and may be explained by assuming either an increased rate of utilization of blood sugar, or a decreased formation of sugar available for blood sugar, or both processes acting together. Soskin and his associates[186] have maintained that there is a decrease in the new formation of sugar from fat because an animal that is fed an adequate amount of protein is able to maintain its blood sugar without the pituitary, but a similar animal, if kept on a fat diet, is unable to do so. They conclude that the normal fasting animal derives its sugar from both fat and protein, whereas the animal without the pituitary is able to convert only protein to carbohydrate. Since the supply of protein is limited, the animal soon becomes hypoglycemic. In contrast, Russell,[174] on the basis of respiratory quotient data, has maintained that more carbohydrate is oxidized following removal of the pituitary. Her results are summarized in Table LV.

From Table LV, it may be seen that the hypophysectomized animals absorbed less glucose, had a lower blood sugar and less deposition in muscles and liver and showed a decreased utilization of oxygen. There was a slight elevation of the respiratory quotient. The fact that the total oxygen consump-

TABLE LV

CARBOHYDRATE OXIDATION AND DEPOSITION FOUR HOURS AFTER FEEDING GLUCOSE TO FASTED RATS (RUSSELL[174])

CONDITION	GLUCOSE ABSORBED MG. PER 100 GM. BODY WT.	O_2 CONSUMPTION ML. PER 100 GRAMS BODY WT. PER HOUR	R.Q.	BLOOD GLUCOSE MG. PER CENT	LIVER GLYCOGEN MG. PER 100 GM. BODY WT.	MUSCLE GLYCOGEN MG. PER CENT
Normal, unfed	—	154	0.72	72	1.2	524
Normal, fed glucose	854	147	0.86	132	123	762
Hypophysectomized, fed glucose	568	106	0.91	79	28	520

tion of the animals without the pituitary is lowered can only mean that all their metabolic processes are slowed down. Therefore, it is difficult to accept the idea that the oxidation of carbohydrate is speeded up in such animals. A shift in the respiratory quotient from 0.86 to 0.91 is not sufficient evidence on which to base the assumption that more carbohydrate is oxidized in the absence of the pituitary gland. It is therefore more logical to assume that some process, such as the new formation of sugar from protein or fat, is inhibited.

The "Houssay Animal."—The finding of Houssay that the removal of the pituitary in addition to the pancreas reduces the symptoms of diabetes has been confirmed by many workers and extended to many dissimilar species. The essential findings in such a preparation have been summarized by Russell[173] as follows:

1. Blood glucose levels are normal.
2. Glucose excretion is much less than in depancreatized animals.
3. No ketonuria is found.
4. Survival is prolonged.
5. Glucose tolerance curves may be normal.
6. Fed glucose is retained.
7. The R.Q. rises after feeding of glucose.
8. Urinary nitrogen is less than in depancreatized dogs.
9. Glycogen is found in the liver in normal amounts.
10. Diabetes returns if anterior pituitary extract is given.

These results demonstrate that there is a balance between the activity of the pituitary gland and the pancreas on carbohydrate metabolism. The removal of the insulin control allows the blood sugar to rise; the removal of the pituitary control brings about a fall in the blood sugar; but the removal of both glands causes the animal to maintain a normal level. The explanation of these results depends on the final interpretation of the activity of these hormones: whether they act through the oxidative mechanisms for using carbohydrate, through the chemical mechanisms for gluconeogenesis, or through the storage mechanisms for carbohydrate.

The "Houssay animal" is produced only by removal of the anterior lobe, not by ablation of the posterior lobe.

Diabetes From Injection of Anterior Pituitary Extracts.—Another outstanding discovery in this field has been the production of permanent diabetes

in a dog through the injection of anterior pituitary extracts. From the anterior lobe of the pituitary body Houssay and Biasotti[146] isolated a hormone which increases the blood sugar on injection. Using a similar preparation, Young[200] has produced in a dog diabetes which continues long after the cessation of the injections. Curiously enough, these dogs are able to survive for long periods without insulin.

On histological examination of the pancreas in these animals the islets of Langerhans are found to be degenerated. Probably the high blood sugar produced by the injection of the anterior pituitary extract brings about these degenerative changes. Homans[145] and Allen[101] showed that, following removal of part of the pancreas, the islet cells of the remainder of the pancreas degenerated. Recently, Woemer[197] has infused glucose solution into guinea pigs for periods as long as twenty-eight days. In some of his animals there was destruction of the beta cells in the islets, with a compensatory increase of islet tissue. No marked glycosuria developed in these animals. The results demonstrate that, if the entire pancreas is intact, the increase of islet tissue compensates for the destruction, whereas if part of the pancreas is removed, the increase is so small that destructive changes predominate and diabetes results. More recently, Lukens and Dohan[156] have shown that cats may also be made diabetic by injection of anterior pituitary extracts, provided that one-half to three-fourths of the pancreas is removed before the injections. These animals show a recovery when insulin is given for periods of nine to thirty-two days. Lukens and Dohan describe a marked hydropic degeneration of the islets of Langerhans in the untreated cats, while the insulin-treated cats had normal islets. These results show clearly the balance between pituitary extract and insulin, and suggest that insulin therapy may bring about complete recovery in the diabetic condition provided that the treatment is started early.

The Relation of the Adrenal Cortex to Carbohydrate Metabolism

Many different types of experimentation have demonstrated that the adrenal cortex plays a role in carbohydrate metabolism. Britton[114] has summarized the carbohydrate changes resulting from various types of operations in cats. His results are given in Table LVI. This type of experimentation has re-

TABLE LVI

CARBOHYDRATE CHANGES IN ADRENAL INSUFFICENCY AND OTHER CONDITIONS IN CATS (BRITTON[114])

	PER CENT CHANGE FROM NORMAL CARBOHYDRATE CONTENT		
	Serum sugar	Liver glycogen	Muscle glycogen
1. Adrenalectomized	−34	−94	−51
2. Pancreatectomized	+586	−80	−28
3. Adrenalectomized-pancreatectomized	−16	−88	+11

vealed that a cat deprived of its adrenal glands loses the ability to maintain a normal blood sugar level and to store glycogen in its muscles and liver. Long and his associates[62] have shown that the fall in these variables is dependent on the duration of starvation following adrenalectomy (Table LVII). It may be seen in this table that the differences between the carbohydrate metabolism of the normal and adrenalectomized animals become greater as the duration of the fasting progresses. Injection of active endocrine preparations from

Table LVII

The Effect of Cortical Extracts on the Carbohydrate Metabolism of Rats (Long[154])

PERIOD OF INJECTION (HOURS)	LENGTH OF FAST (HOURS)	TOTAL CORTICAL EXTRACT ML.	GLYCOGEN PER CENT		BLOOD GLUCOSE MG. %	REMARKS N = NORMAL A = ADRENAL-ECTOMIZED
			LIVER	MUSCLES		
0	24	0	0.206	0.508	63	N
0	24	0	0.016	0.432	54	A
0	48	0	0.233	0.507	80	N
0	48	0	0.070	0.358	30	A
8	32	8	0.848	0.521	95	N
11	35	11	0.652	0.421	--	A
12	36-54	12	1.644	0.536	95	N
12	48	12	1.778	0.411	93	A

Table LVIII

Carbohydrate Changes in Adrenal Insufficiency in Rats Following Starvation (Long[154])

CONDITION N = NORMAL A = ADRENAL-ECTOMIZED	DURATION OF FASTING HOURS	BLOOD SUGAR MG. PER CENT	LIVER GLYCOGEN PER CENT	MUSCLE GLYCOGEN PER CENT
N	0	124	1.78	0.590
A	0	97	2.31	0.530
N	24	72	0.025	0.520
A	24	54	0.016	0.432
N	48	80	0.233	0.507
A	48	30	0.070	0.358

the adrenal cortex will restore the blood sugar and liver glycogen to the normal level (Table LVIII). Muscle glycogen is restored also if adequate glucose is given to the animal.

With the rise in liver glycogen in the treated adrenalectomized animal there is a corresponding increase in urinary nitrogen, a phenomenon which demonstrates that the extra sugar is formed from protein (Long[154]). This mechanism, however, is not sufficiently active to restore muscle glycogen. In order to bring this compound back to its normal value, glucose must be ingested by the animal. It is difficult to understand why the liver in the treated fasting animal holds its newly formed glycogen and does not liberate it for utilization by the muscles. Hartman[142] and Long and Lukens[153] have shown that the typical symptoms of diabetes following removal of the pancreas do not develop if the adrenal glands are also removed. Adequate replacement therapy by injection of adrenal cortical extracts restores the diabetic syndrome (Long[154]). The explanation of this finding may be that the removal of the adrenal glands produces a condition in which proteins may not be converted into carbohydrate. Since this is one of the mechanisms for the production of the high blood sugar in diabetes, the inhibition of this mechanism lowers the blood sugar to the normal condition.

The Relation of the Thyroid Gland to Carbohydrate Metabolism

It is well known that patients suffering from thyroid disturbances show alterations in their carbohydrate metabolism. When hyperthyroidism accompanies diabetes mellitus, the severity of the symptoms of this disease increases.

Dohan and Lukens[126] have investigated the effects of the surgical removal of both the thyroid gland and the pancreas in cats. Their results are given in Table LIX.

TABLE LIX

THYROIDECTOMIZED-DEPANCREATIZED CATS (DOHAN AND LUKENS[126])

	WEIGHT KG.	GLUCOSE GM./KG./DAY	NITROGEN GM./KG./DAY	KETONES MG./KG./DAY
Depancreatized	2.66	3.21	1.31	111.0
Depancreatized Thyroidectomized[1]	2.57	2.45	1.04	56.7
Depancreatized Thyroidectomized[2]	2.98	2.70	1.06	63.8

[1]Thyroidectomy done four to thirty-four days before pancreatectomy.
[2]Thyroidectomy done at the same time as pancreatectomy.

In Table LIX, it may be observed from the results that the removal of both the thyroid and the pancreas decreases the output of glucose, nitrogen, and ketones. These effects are not surprising, for in an animal lacking both the thyroid and the pancreas, the metabolic rate is lowered and, therefore, the velocity of all processes in the body is reduced. Rudy, Blumgart and Berlin[172] have described a case of diabetes which could not be controlled by 95 units of insulin daily. Following removal of the thyroid gland, however, 44 units of insulin were adequate for complete control of the diabetic condition. Administration of thyroid extract brought back the symptoms existing before the operation.

Additional proof that the thyroid affects carbohydrate metabolism has been supplied by Soskin, Levine and Heller.[188] These authors showed that injections of thyroid extract into a hypophysectomized animal increased the blood sugar to the normal level. This level could be maintained as long as the injections continued. With this increase in blood sugar, there was a corresponding increase in the output of urinary nitrogen. Therefore, increasing the metabolic processes in general increases the breakdown of protein. This, in turn, supplies new-formed carbohydrate to maintain a normal blood sugar level. The secondary atrophy of the thyroid gland which results from removal of the pituitary gland may play a role in the disturbances in carbohydrate metabolism produced by hypophysectomy.

CHAPTER LII

THE CHEMISTRY OF MUSCULAR CONTRACTION

SKELETAL MUSCLE

When muscles contract, the energy put out in doing mechanical work, or as heat, is derived from certain chemical transformations which take place within the muscle fibers. Thus a muscle may be regarded as a machine which transforms chemical energy into work. The magnitude of the chemical changes and the amount of work done during a series of contractions may be measured, but as yet the mechanism of this conversion is unknown. Numerous levers have been devised for following accurately the time course of the tension developed during muscular contraction. There are, however, no methods sufficiently accurate and rapid to permit a study of the chemical changes which accompany and follow a single twitch. In fact it is necessary to stimulate a muscle for several seconds before any chemical conversion can be detected and in the case of some reactions the muscle must be completely fatigued before changes sufficient to permit analysis take place. A complete knowledge of the chemistry of muscular contraction would embrace a description of the chemical events underlying (a) the contraction heat, (b) the relaxation heat, (c) the delayed oxidative heat, and (d) the delayed anaerobic heat. Our present knowledge of these matters is fragmentary although certain relevant facts have come to light.

In the study of the intermediate processes occurring during and after contraction, the following procedures have been employed: (1) electrical stimulation under aerobic and anaerobic conditions; (2) application of pharmacological agents which block certain chemical reactions; (3) isolation of enzyme systems from muscle to demonstrate that certain reactions are possible; (4) addition of chemical substances to minced muscle to study the capacity of the system to convert them to other compounds; (5) grinding of muscle tissue to determine the maximal change in response to injury; and (6) application of radioactive isotopes. On the basis of the results of these diverse lines of investigation attempts have been made to describe the *sequence* of chemical events which occurs during a single contraction. In this chapter, however, the known facts concerning the chemical changes which may provide the chief sources of energy for contraction will be emphasized. Considering the present state of our knowledge, it would be premature to attempt to correlate in any detail the chemical with the thermal and mechanical aspects of contraction. The facts will stand; the sequence and relative importance of the different reactions can be firmly established only by further progress.

Respiratory Metabolism

From a practical point of view, the most important changes which take place in a muscle during a series of contractions are the *aerobic processes.* Although a muscle is able to do a small amount of work in the absence of oxygen, it must have an adequate supply to insure complete recovery. There-

fore, much more external work may be obtained under aerobic than under anerobic conditions. An example of the great differences in energy output was obtained by Hill and Kupalov.[227] A sartorius muscle in Ringer's solution in oxygen contracted more than 10,000 times before fatigue, whereas in nitrogen the muscle underwent only 2,500 twitches.

A measurement of the oxygen consumption of a muscle enables an observer to calculate the total energy needed by that muscle during work and to compare this energy to the external work. This comparison gives the efficiency of a muscle. Another relationship, the respiratory quotient, has also been used in an attempt to evaluate the type of food material consumed in muscular metabolism.

Methods for Measuring Oxygen Consumption.—It is of interest to discuss the various methods which have been devised to measure the oxygen consumption of resting and active muscles, especially as these procedures have a general application to all organs. For small muscles or sections of tissue, the Warburg apparatus is used most commonly. In this method, the volume is controlled by a change in pressure. The amount of pressure needed to restore the gas system to its original volume is determined, and, by the use of suitable constants, this pressure reading may be converted into volume units. In contrast to the manometric method, the volumetric method measures the volume change directly. These methods have been described in detail by Dixon.[209]

The chief limiting factor in the use of these methods is the thickness of the tissue, for if it is too thick, oxygen cannot diffuse into all parts of the tissue and thus the experiment becomes a partially anaerobic procedure. Hill[226] has calculated from the utilization of oxygen and the rate of diffusion of oxygen into muscular tissue that a sartorius muscle 0.5 mm. thick would be able to contract once every two seconds without going into an "oxygen debt." Later, Hill and Kupalov[227] put these calculations to an experimental test. The results of their experiments are given above.

To obtain the oxygen consumption of a muscle in the intact animal, the usual procedure is to measure the oxygen content of the blood entering and leaving the muscle as well as the rate of blood flow. The difference between the first two determinations gives the oxygen absorbed from every milliliter of blood passing through the organ. This difference multiplied by the amount of blood which flows through the organ in a given time gives the oxygen consumption in that time. Examples of such calculations from the work of Himwich and Castle[225] are given in Table LX.

TABLE LX

OXYGEN CONSUMPTION OF MUSCLE (HIMWICH AND CASTLE[225])

WEIGHT OF ANIMAL KG.	TEMP. OF MUSCLE ° C.	WEIGHT OF MUSCLE GM.	BLOOD FLOW PER HOUR PER GRAM MUSCLE ML.	O_2 USED PER 100 ML. BLOOD ML.	O_2 USED PER HOUR PER GRAM MUSCLE ML.
23.31	39.4	110	4.08	5.33	0.217
16.12	38.0	72	9.42	2.44	0.230
14.57	41.7	64	7.98	7.22	0.576

Recently, Millikan[239] has used the reduction of muscle hemoglobin as an indicator for oxygen consumption in muscle. This method has the advantages of employing an intracellular compound which occurs naturally in muscle and

of having a very small temporal lag. With suitable optical recording, the latter factor may be reduced to 0.2 sec. Quensel and Kramer[242] have also used an optical method. In theirs the degree of reduction of the venous blood which had flowed through the muscle was determined by means of a photocell. This method has a longer temporal lag than Millikan's because the blood has to pass through the capillaries into the veins before the amount of reduction is measured.

Some of the results obtained by these various methods are given in Table LXI.

TABLE LXI

OXYGEN CONSUMPTION OF RESTING AND STIMULATED MUSCLES

MUSCLE	ANIMAL	ML. O_2 PER GRAM PER HOUR		OBSERVER
		RESTING	WORKING	
Sartorius	Frog	0.017	0.275	Gemmill
Gastrocnemius	Dog	0.36	2.22	Himwich
Soleus	Cat	0.21	4.752	Millikan
Gastrocnemius	Dog	0.53	3.54	Kramer

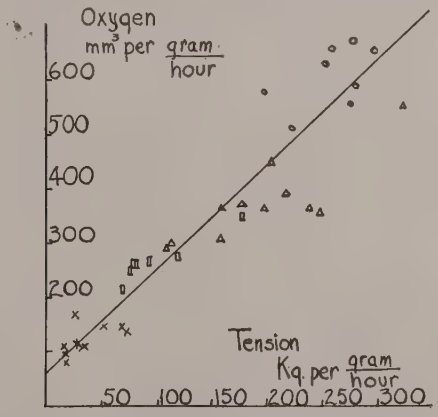


Fig. 288.—Graph showing the relationship between the tension developed and the oxygen consumed in the isolated sartorius muscle of the frog. Results of four series of experiments. (From Gemmill: Am. J. Physiol. 115: 371, 1936.)

From Table LXI, it may be seen that the oxygen consumption of a muscle is increased considerably by stimulation.

There are several factors which influence the oxygen consumption of muscle. The chief factor is the amount of work carried on by the muscle. A graphic summary of experiments correlating the tension developed in isometric contractions with the oxygen used is given in Fig. 288. It may be seen from this figure that there is a correlated increase in oxygen consumption with the increase in tension developed. A similar relationship between the amount of work performed and the oxygen consumed has been observed during moderate muscular exercise in man (see Chapter LVIII). Another factor is the initial tension; more oxygen is used at high than at low tensions under resting conditions. Since a muscle responds with a greater force of contraction at high

initial tensions than at low, it is natural to assume that the greater force of contraction would require more oxygen. This fact was observed experimentally by Fischer.[214] Therefore, the load lifted by a muscle during work affects oxygen consumption.

Efficiency of Muscular Contraction.—The relationship between the input of energy and the output gives the mechanical efficiency of any process. The efficiency of a muscular contraction has been calculated from the measurement of energy developed during isotonic contractions and the oxygen utilization. From such determinations, Fischer[214] obtained efficiencies varying from 4.1 to 13.8 per cent, with an average of 9.0 per cent. The value varies with the load, there being an optimal load for each muscle which gives maximal efficiency. The average value agrees with the efficiencies determined by Fenn[213] from heat production measurements. These determinations showed that an isolated sartorius muscle from a frog had an oxidative efficiency of 10 to 12 per cent.

Respiratory Quotient.—The respiratory quotients of resting and stimulated muscles have been determined by many observers. A summary of their results is given in Table LXII. One of the earliest studies was that of Meyerhof[236] on muscles during the recovery period. Four different sets of muscles were used in order to obtain sufficient data for the calculations of the quotient. The conditions of these experiments have been overlooked by subsequent writers who have claimed, on the basis of Meyerhof's results, that the respiratory quotient of the contracting isolated muscle is always 1.00 and that therefore the oxidation of carbohydrate supplies the sole source for the energy used in the muscular contraction. However, his results simply indicate that the quotient of the recovery period following tetanic stimulation may be unity. The more recent values (Table LXII) obtained on muscles from different animals

TABLE LXII

RESPIRATORY QUOTIENTS OF RESTING AND CONTRACTING MUSCLES

ANIMAL	R.Q.		OBSERVER
	RESTING	WORKING	
Frog	1.06	1.02	Meyerhof
Frog	0.91	0.91	Fenn
Frog	0.80	0.90	Gemmill
Dog	0.77	0.81	Himwich

demonstrate that the quotient for both the resting and contracting muscle is less than unity when the muscle is under aerobic conditions. This fact, taken into consideration with additional findings discussed in the next section, demonstrates that the muscle may use a mixture of food material in order to obtain aerobic energy for muscular contraction.

Mechanisms for the Utilization of Oxygen by Muscle.—The question of the methods by which a muscle uses oxygen and gives off carbon dioxide will now be discussed in terms of the oxidative enzyme systems (see Chapter XLVIII) present in the muscle and their application to the contracting muscle. Numerous types of experimentation have shown that the cytochrome-cytochrome oxidase system is present and active in muscular tissue. Muscle gives a strong indophenol oxidase reaction. Its respiration is cyanide and carbon monoxide sensitive and bands of reduced cytochrome appear under anaerobic conditions. In his original paper on cytochrome, Keilin[29] described the appearance of these

bands in the wing muscles of a moth on contraction. These bands disappeared when the moth stopped struggling. Urban and Peugnet[248] have observed the bands of reduced cytochrome appearing after contraction in the sartorius muscle of a frog. Moreover, Stannard[246] has made the interesting observation that sodium azide inhibits the oxygen consumption during tetanic stimulation but does not diminish the metabolism of resting muscle. Since azide inhibits the cytochrome-cytochrome oxidase system these experiments give additional evidence that this system carries the burden of the oxidative processes during tetanic contraction in which lactate is formed. The application of carbon monoxide as an inhibitor to muscular respiration is complicated by the fact that muscle has the property of oxidizing carbon monoxide. Nevertheless, Stannard[247] has shown that light reverses the inhibited respiration of muscle in the presence of carbon monoxide. This fact indicates that the characteristic reaction of carbon monoxide with the respiratory enzyme occurs in muscle.

Muscle is very rich in dehydrogenases; in fact, in most of the original work of Thunberg on these enzymes muscle was used as the enzyme source. Dehydrogenases of lactate, hydroxybutyrate, succinate, malate, citrate, tartrate, glutamate, and glycerophosphate have been demonstrated to be in muscular tissue. Muscle also has a rich supply of the coenzymes, DPN and flavine nucleotides.

These oxidative mechanisms work very efficiently. The reduced bands of cytochrome appear very quickly following stimulation. The reduction of muscle hemoglobin occurs 0.2 second after contractions have started (Millikan[239]). Using a very sensitive volumetric apparatus, Hill[228] has shown that the oxygen consumption of a stimulated muscle occurs mainly after the contraction is over. These facts demonstrate that during contraction, the general level of the oxidation-reduction potential in the muscle shifts towards the more reduced state and is only pulled back again by direct intervention of molecular oxygen.

Carbohydrate Metabolism

The metabolism of *carbohydrate* in muscle begins with glycogen [$(C_6H_{10}O_5)_n$] and ends with the products of the combustion of this substance. Most of the work on the chemistry of muscular contraction deals with this carbohydrate, the intermediate products of its breakdown, the oxygen used in its combustion and the final production of carbon dioxide and water.

The exact chemical nature of glycogen is not known. It is related to the higher dextrins and like them gives a brownish-red color with iodine. Unlike the dextrins it forms strongly opalescent solutions in water. Recent work has shown that muscle glycogen is composed of unbranched chains of twelve glucose units. It apparently exists in more than one form and the name "glycogen" is used more in terms of a standard method for its detection than to signify a definite chemical compound.

In the study of the metabolism of muscle glycogen numerous factors must be taken into consideration. The principal ones have been enumerated by Macleod[234] as follows: (1) species and age of the animal; (2) previous diet; (3) duration of fasting; (4) condition of the ductless glands; (5) season of the year; (6) cyclic changes; (7) the state of the animal (anesthesia, blood pressure, anoxemia, stunning); and (8) post-mortem changes. These factors are of special importance when one considers glycogen changes in mammalian muscle. Fortunately, to obtain comparable results with frog muscle it is sufficient to keep the tissue cold during the preparation and stimulation.

Using frog muscle Meyerhof[237] studied the disappearance of glycogen immediately after a period of contraction and its subsequent reappearance during

rest. On stimulating for thirty minutes at the rate of sixty a minute, he found a decrease in glycogen (reported as glucose) from 10.3 mg. per gram of muscle to 7.2 mg. In another experiment he stimulated two sets of muscles for fifteen minutes, analyzed one set for glycogen immediately after stimulation and the other set twenty-three hours later. The recovery group of muscles had 1.38 mg. more glycogen per gram than the first set. Experiments of this type give direct evidence that glycogen disappears during continued contraction and reappears in the recovery period. Cori and Cori[208] followed these changes in rat muscle with circulation intact. Their average results are given in Table LXIII. They confirm the results that Meyerhof obtained with frog muscle; namely, the disappearance of glycogen on stimulation and its partial return during oxidative recovery.

TABLE LXIII

DISAPPEARANCE OF GLYCOGEN DURING STIMULATION AND ITS RECOVERY AFTER STIMULATION (FROM CORI AND CORI[208])

Gastrocnemius muscle of fasting rats stimulated for fifteen seconds. Values are in milligrams of glucose per 100 grams of muscle. Each figure represents the average of the results of a number of experiments (number in parentheses) in which the muscle from one side was compared with that from the other side.

RESTING	STIMULATED	RECOVERY	
		10 MINUTES	20 MINUTES
549 (8)	356 (8)	—	—
—	296 (9)	350 (9)	—
—	—	295 (4)	339 (4)

With the disappearance of glycogen during stimulation, there is an augmentation in the hexosephosphate content (Cori and Cori[208]). This reaction is reversible, for during the recovery period, the hexosephosphate content decreases.

Lactate.—The lactate ($CH_3CHOHCOO^-$) of biological importance is the dextro-rotatory form of α-hydroxy propionate. Although analyzed and reported as lactic acid, very little non-ionized lactic acid exists at the pH of the body fluids; the greater part of this acid is ionized into lactate ions and hydrogen ions. Therefore in this chapter, the term *lactate* will be used in place of the more common but incorrect term "lactic acid."

Since the isolation of this substance from muscle by Berzelius in 1807, lactate has been associated with the chemical events underlying contraction. The precise conditions of its formation were not recognized, however, until Fletcher and Hopkins[218] in 1907 published their now classical paper on this subject. They found that resting frog muscle contains very little lactate (0.015 to 0.023 per cent), that mechanical injury, heat, or chloroform raises the lactate content, and that stimulation under anaerobic conditions induces a very considerable increase over the resting level (to 0.3 per cent). Finally, they demonstrated that during recovery in oxygen, the lactate is removed. Fletcher and Hopkins suggested that lactate, which formed anaerobically during contraction, may be oxidized or built back into its precursor during recovery. By comparing the oxygen consumed with the amount of lactate disappearing during aerobic recovery, Meyerhof,[238] in 1920, calculated that three to four molecules of lactate are reconverted to glycogen for every one that is oxidized. He concluded that part of the lactate or an equivalent amount of carbohydrate is burned to supply the energy for the re-formation of glycogen from lactate.

Evidence has been obtained that the lactate which appears under anaerobic conditions is derived from glycogen by a series of reactions in which oxygen is, of course, unnecessary.

It was first assumed that lactate is formed before or during the actual contraction of the muscle. Embden and his associates,[212] however, showed that part of the lactate is formed after the contraction. This observation has been confirmed by several observers, and it is now generally accepted that much of the lactate is produced after contraction and relaxation are over. Consequently, the formation of this substance is not a reaction from which energy for contraction is immediately derived.

A theoretical discussion by Hill[226] of the diffusion of oxygen and lactate through muscle tissue followed and in turn provoked new experiments. Hill calculated that a frog's sartorius muscle suspended in Ringer's solution can contract anaerobically six times a minute without appreciable accumulation of lactate. The lactate would have sufficient time to diffuse out into the solution

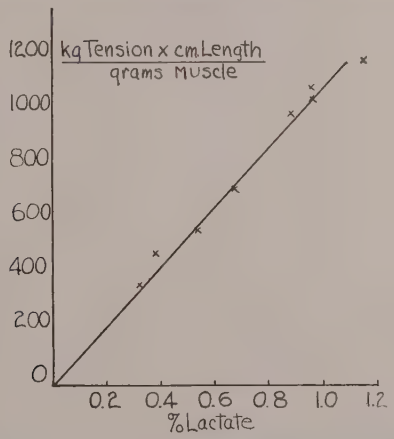


Fig. 289.—Relationship between lactate production and tension developed in isolated muscle. Abscissa, lactate per cent; ordinate, $\frac{\text{kg. tension} \times \text{cm. length.}}{\text{grams muscle}}$. (From Gemmill: Biochem. Ztschr. 246: 319, 1932.)

and never reach a "fatigue level" in the muscle. To test this calculation experimentally, Hill and Kupalov[227] mounted muscles in oxygen-free Ringer's solution and stimulated them once every eleven seconds. These muscles continued to contract for eight hours. When rapid rates of stimulation (60 a minute) were used, fatigue ensued very quickly. Gemmill[220] measured the amount of lactate developed by muscles stimulated at low frequencies in oxygen-free Ringer's solution and found a direct proportion between the lactate production and tension developed (Fig. 289). There can be no doubt that the production of lactate is associated either directly or indirectly with the development of tension under anaerobic conditions.

The question which now arises concerns the production of lactate under aerobic conditions. During short periods of tetanic stimulation, a muscle in oxygen may give rise to some lactate. This fact has been demonstrated by

Sacks, Sacks and Shaw[243] in cats' muscles (Table LXIV). It must be realized, however, that stimulation under such conditions may demand a need for oxygen greater than the oxygen supply, and thus a muscle may actually be responding anaerobically even though the arterial blood entering the muscle capillaries is fully oxygenated. From calculations of the oxygen supply in a muscle, it seems certain that a single twitch may be carried out under full aerobic conditions. Unfortunately, available chemical methods are not sufficiently sensitive to detect small changes in lactate content which may take place as a result of such a contraction. The evidence which bears on this question is very indirect and involves the question as to whether lactate is always an intermediate in carbohydrate metabolism or whether carbohydrate may be oxidized directly without going through a lactate stage. Any student interested in this complex subject should consult the article on "The Pasteur-Meyerhof Reaction" by Burk.[207]

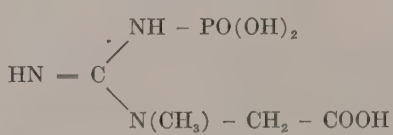
TABLE LXIV

PHOSPHATE COMPOUNDS AND CARBOHYDRATE CHANGES IN MUSCLE DURING CONTRACTION (SACKS, SACKS AND SHAW[243])

Values expressed as mg. per cent of P and of lactate. Carbohydrate changes calculated as mg. per cent of glucose. Stimulation at rate of 1 per sec.

STIM. TIME MIN.	PHOSPHO-CREATINE HYDROLYZED	ADENYL PYRO-PHOSPHATE HYDROLYZED	HEXOSE PHOSPHATE FORMED	INCREASE IN LACTATE	CARBOHY-DRATE BALANCE	WATER UPTAKE
1	22	0	2.0	62	−30	2
2	37	0.3	0.5	93	−74	8
5	39	2.0	1.0	137	−77	12
10	28	0	0.6	80	−92	11
30	32	16	1.0	103	−574	20

Phosphate Metabolism.—For a long time, it was suspected that phosphate was involved in the chemical transformations which underlie muscular activity. It was not until 1927, however, that the importance of an organic compound of phosphate was clearly demonstrated. In that year Fiske and Subbarow[215] in America and Eggleton and Eggleton[210, 211] in England showed independently the existence of an unstable organic compound containing phosphate in muscle. Its chemical nature was first determined by the former pair of workers who called the compound *phosphocreatine:*



The work of these authors showed conclusively that with continuous muscular contraction phosphocreatine breaks down, and during the recovery period, is re-formed. The evidence for this is given in Table LXV-A. Nachmansohn[240] observed that even under anaerobic conditions, there is some resynthesis of phosphocreatine during recovery. The biological importance of this substance was not fully recognized until Lundsgaard[231-233] demonstrated that under a pharmacological condition, the breakdown of phosphocreatine supplied energy for muscular contraction. By poisoning muscles with monoiodoacetate, he was able to obtain the breakdown of phosphocreatine with inhibition of lactate for-

TABLE LXV-A

EFFECT OF STIMULATION AND RECOVERY ON PHOSPHOCREATINE CONTENT OF MAMMALIAN MUSCLE (SLIGHTLY MODIFIED FROM FISKE AND SUBBAROW[217])

			PHOSPHOCREATINE P	INORGANIC P
AVERAGE FIGURES OF 16 DETERMINATIONS ON 8 DIFFERENT NORMAL RESTING MUSCLES			MG. PER CENT 65 (55-86)	MG. PER CENT 26 (18-35)
STIMULATION	RECOVERY	NAME OF MUSCLE		
Intermittent Tetanization of Nerve				
10 min.		Gastrocnemius	24	65
25 min.		Gastrocnemius	34	39
25 min.		Biceps	21	66
Continuous Tetanization of Nerve				
5 sec.		Gastrocnemius	33	52
10 sec.		Gastrocnemius	29	54
20 sec.		Gastrocnemius	24	58
3 min.		Gastrocnemius	17	55
6 min.		Gastrocnemius	16	57
30 min.		Gastrocnemius	11	69
9 min.		Biceps	2	84
12 min.		Biceps	0	82
Completely Fatigued With Artery Clamped				
4 min.		Biceps	0	77
4 min.		Gastrocnemius	0	70
4 min.		Gastrocnemius	0	74
Recovery (after complete fatigue) With Circulation Restored				
	25 min.	Biceps	41	28
	25 min.	Biceps	41	27
	1 hr.	Gastrocnemius	46	19

mation (Table LXV-B). He found that the phosphate from the phosphocreatine was transferred to a hexose to form hexosephosphate. He discovered also that the amount of phosphocreatine broken down was proportional to the energy liberated. These two facts led Lundsgaard to suggest that the mechanical energy developed by a muscle was related to the energy liberated from the breakdown of phosphocreatine. It is true, nevertheless, that when lactate is formed, as in an unpoisoned muscle, tension is obtainable over a longer period of time than when its formation is blocked by monoiodoacetate. In this connection, it is interesting to note that a poisoned muscle does more work when lactate is supplied externally under aerobic conditions (Mawson[235]).

TABLE LXV-B

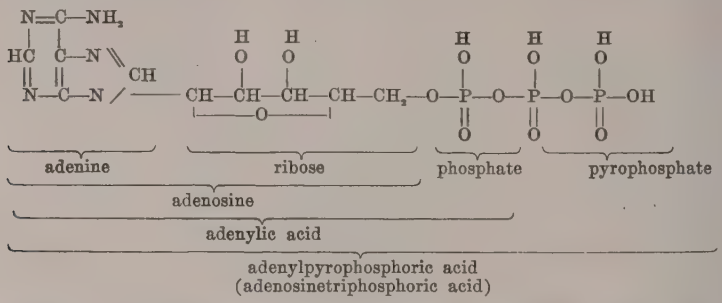
THE BREAKDOWN OF PHOSPHOCREATINE IN NORMAL MUSCLES AND IN MUSCLES POISONED WITH MONOIODOACETIC ACID (FROM LUNDSGAARD[231])

Lactic acid in mg. per cent; phosphorus compounds in mg. per cent phosphorus.

CONDITION OF MUSCLE		LACTIC ACID	PHOSPHORIC ACID	PHOSPHOCREATINE
Normal	Resting	25	21	61
	Working	84	29	46
Poisoned	Resting	16	29	57
	Working	15	28	0

Another phosphate compound of importance is *adenylpyrophosphate.* As in the case of phosphocreatine, the structure and importance of this substance

have been discovered only during recent years. Lohmann[230] has determined the chemical structure of this compound. It is composed of adenine, ribose, pyrophosphate and phosphate:



Lundsgaard[233] and Sacks[243] have shown that this substance breaks down after long periods of stimulation.

Glycolysis.—In the above sections, evidence was presented that during contraction under aerobic and anerobic conditions, glycogen disappears, and that under anaerobic conditions lactate appears. Two phosphate compounds, phosphocreatine and adenylpyrophosphate, are broken down following long periods of contraction. The question now arises as to the relationships of these events. In enzymatic solutions, a definite scheme may be given for the relationships of these compounds to each other. The chief reactions in this scheme are given in Table LXVI. Inorganic phosphate is needed to form the hexosemanophosphate (Reaction 1). Adenylpyrophosphate supplies phosphate to the hexosephosphate to form the hexosediphosphate (Reaction 2). The hex-

TABLE LXVI

SCHEME OF GLYCOLYSIS

REACTION	ENZYME	COENZYME
1. Glycogen + Phosphate → Hexosemonophosphate	Phosphorylase	Adenylic acid
2. 2 Hexosemonophosphate + Adenylpyrophosphate → 2 Hexosediphosphate + Adenylic Acid	Phosphorylase	Mg++
3. Hexosediphosphate → 2 Triosephosphate	Aldolase	
4. Triosephosphate → Phosphoglycerate	Triosephosphate Dehydrogenase	DPN
5. Phosphoglycerate → Phosphopyruvate	Enolase	
6. Phosphopyruvate → Pyruvate + Phosphate	Phosphorylase	Adenylic acid
7. Pyruvate → Lactate	Lactate Dehydrogenase	DPN
8. Adenylic Acid + 2 Phosphocreatine → Adenylpyrophosphate + 2 Creatine	Phosphorylase	Mg++
9. Phosphopyruvate + Adenylic Acid → Adenylpyrophosphate + 2 Pyruvate	Phosphorylase	Mg++

osediphosphate breaks down into triosephosphate (Reaction 3) which, in turn, is oxidized to a phosphoglycerate (Reaction 4). In this reaction DPN (see page 715) is necessary. The phosphoglycerate is converted into a pyruvate (Reaction 6) and the final reaction is a conversion of pyruvate to lactate (Reaction 7). In this reaction the DPN is again involved. The association of this coenzyme in the triosephosphate dehydrogenase and lactate dehydrogenase reactions produces a coupled reaction: the first enzymatic reaction reduces the DPN, and the second oxidizes the coenzyme back to its original state. In this condition, it may once again enter into the total reaction. The role of phosphocreatine is to supply phosphate for the reconversion of adenylpyrophosphate (Reaction 8). Phosphopyruvate may act in a similar capacity (Reaction 9).

This remarkable enzymatic scheme has given rise to two schools of thought. The one applies the enzymatic scheme to the contracting muscle and claims that, under anaerobic conditions, lactate is formed from glycogen by the same steps as in the glycolytic scheme. For example, in its formation, hexosediphosphate is formed by Reaction 2, and adenylpyrophosphate is re-formed by a breakdown of phosphocreatine (Reaction 8). The phosphocreatine is re-formed by the breakdown of phosphopyruvate. This theory would explain lactate formation in muscle, and would explain why the phosphocreatine is broken down before the adenylpyrophosphate in the stimulated muscle. Another school of thought maintains that these enzymatic reactions have no direct connection with the chemical events in the muscle. In their original paper Fiske and Subbarow[217] state that phosphocreatine hydrolysis supplies base to neutralize the lactate as it is formed. Thus these two events may not be connected directly but only indirectly. The most recent evidence that the glycolytic scheme does not apply to the stimulated muscle is given by Sacks.[245] Using radioactive phosphorus in the inorganic phosphate, Sacks studied the distribution of this tracer following a short period of contraction. If the scheme of glycolysis were working in a muscle, the tracer element should have been equally distributed throughout the organic phosphate molecules as they acted as donators and acceptors in cyclic processes for the phosphate. On analysis, however, Sacks found that the adenylpyrophosphate did not take up any additional radioactive phosphorus. It was contained chiefly in the hexosemonophosphate portion. Therefore, it was concluded that adenylpyrophosphate under the conditions of these experiments does not enter into the chemical changes during contraction.

It has been recently shown by Flock, Ingle and Bollman[219] that the major changes in glycogen, phosphocreatine, adenylpyrophosphate, hexosephosphate, lactate, and inorganic phosphate occur during the first minute of muscle stimulation (Fig. 290). This may mean that these substances which have been studied so extensively are only used at the beginning of muscular exertion before a steady state is reached. When this latter condition is attained, then other substances are used. The most logical assumption to be made is that glucose from the blood stream is the chief source of energy under these conditions.

Fat Metabolism.—The discovery that an R.Q. of stimulated muscles may be less than unity (Table LXII) and that the quotient of man during exercise may also be less than 1.0 (see Chapter LVII) suggests the oxidation of non-carbohydrate material. A direct comparison of the disappearance of carbohydrate with the total oxygen consumed during a period of stimulation of

frog's muscles has shown that the oxidation of carbohydrate accounted for only a part of the total exchange during this period (Gemmill[222]). These facts demonstrate that in the frog's muscle not all of the energy for aerobic contraction may be derived from the oxidation of carbohydrate. Direct evidence that fat may be used by frog's muscle has been given by Niernierko[241] and Buchwald and Cori.[6] These observers showed that during contraction in frog's muscles taken in the summer when the carbohydrate content was low the fat content decreased. This evidence favors a definite utilization of fat by a muscle of the frog, especially when the carbohydrate supply is diminished. In order to test this question in rats, Gemmill[223] gave phlorizin to a group of these animals with the hope that their carbohydrate store might be reduced and their fat metabolism during contraction augmented. However, even after several days of phlorizin poisoning, the fat content of the stimulated muscle was not decreased. It is well known, however, that exercise diminishes the fat content of an animal's body. If this fat is not used directly, it must be used indirectly. The

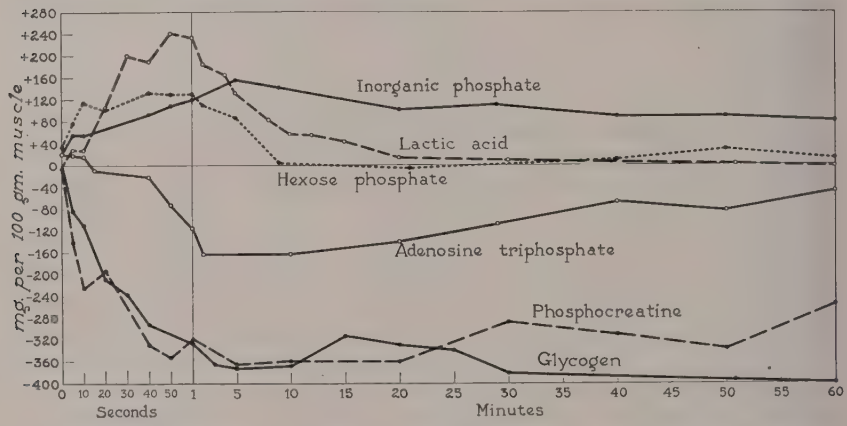


Fig. 290.—Relationship of chemical changes in muscle during continuous contraction at rate of 3 × per sec. expressed as mg. of each substance per 100 grams of muscle. (From Flock, Ingle, and Bollman: J. Biol. Chem. 129: 99, 1939.)

chief indirect method for utilization is through the conversion of fat to acetone bodies and the utilization of the acetone bodies by the contracting muscle (see Chapter LV). Therefore, in animals in which the carbohydrate supply is low or in animals with diabetes, the production of acetone bodies may be very important as a supply of metabolites for energy production by the muscle. Another fatty acid metabolite which may be used by muscle is fumarate (Harrison[224]).

Summary.—From the available evidence concerning the chemical changes occurring during muscular contraction, the following facts are evident. A contracting muscle uses and needs oxygen. The oxygen consumption is proportional to the work done, thus indicating a direct relationship between oxidation and mechanical events. The cytochrome-cytochrome oxidase system is involved in these oxidations. Carbohydrate is used during muscular work and is probably the chief fuel for muscular contraction. Under anaerobic conditions, lactate is formed in amounts proportional to the amount of work done. The interrelation of phosphocreatine, adenylpyrophosphate, and the hexosephosphates in the con-

tracting muscle is not clear although in enzymatic solutions they have a definite relationship. In the contracting muscle, these substances may act only as a reserve store of energy to be used to inaugurate muscular contraction or to be used during severe muscular exertion when the muscles are operating under anaerobic conditions. Even under these conditions the sequence of their utilization by the intact muscle has not been strictly defined. When the carbohydrate supply is low, mammalian muscle may use acetone bodies for energy production. Thus fats may be used indirectly for the production of muscular energy.

SMOOTH MUSCLE

Although the chemical changes in smooth muscle during rest and activity have not been as thoroughly studied as in skeletal muscle, certain similarities and several differences have been detected in the metabolisms of these two tissues. The oxygen consumption of resting smooth muscle is less than that of cross-striated muscle. In his review of the results on oxygen consumption for various tissues, Krebs[249] reports values for the Qo_2 ($mm.^3$ of O_2 per mg. dry weight per hour) varying from –1.3 to –3.8 for smooth muscle, while for the diaphragm, a representative cross-striated muscle, a value of –6.0 was recorded. There is very little augmentation in oxygen consumption during tonic activity although the presence of oxygen is necessary for the continued maintenance of tone (Evans[250]). On oxygenation after an anaerobic period, there is an increase in oxygen utilization, demonstrating that intermediate metabolites accumulate during that period. The chief intermediate is lactate and this substance increases in smooth muscle under anaerobic conditions, on stimulation and on mincing in alkali.

Since glycogen has been shown to disappear from smooth muscle under anaerobic conditions, it is obvious that the carbohydrate changes are very similar to those in cross-striated tissue. Data for these facts are given in Table LXVII.

TABLE LXVII

CHEMICAL CHANGES IN SMOOTH MUSCLE (EVANS[250])

CHEMICAL COMPOUND	CONDITION OF MUSCLE	BEFORE PER CENT	AFTER PER CENT	DIFFERENCE
Lactate	4.5 hours in N_2	0.016	0.092	+0.076
Glycogen	4.5 hours in N_2	0.151	0.100	–0.051
Lactate	1 hour stimulation	0.029	0.085	+0.056
Lactate	Minced in alkali	0.025	0.087	+0.062
Lactate	4.5 hours in N_2	0.016	0.079	+0.063
Glycogen	Recovery, 19 hours in O_2	0.151	0.122	–0.029

Creatinephosphate occurs in smooth muscle of vertebrates and argininephosphate in the smooth muscle of invertebrates. The phosphocreatine content of smooth muscle decreases on stimulation and increases during an aerobic recovery period (Eggleton[251]). No such recovery occurs under anaerobic conditions.

CARDIAC MUSCLE

In contrast to skeletal muscle which is normally permitted long periods of rest, the heart must beat rhythmically during the entire life of an animal. It has been calculated (Evans[254]) that during the lifetime of an average man, the heart beats 2,600 million times, pumping out at least 150,000 tons of blood from

each ventricle. Therefore, it becomes of great interest to determine the sources of energy for this organ which develops such an output of work and to compare its metabolism with that of skeletal muscle.

The fundamental difference between the metabolic activity of skeletal and cardiac muscle is that skeletal muscle has the ability to go into an oxygen debt which may be repaid during a recovery period but cardiac muscle must complete its metabolic events during each cardiac cycle. Its recovery period may not be more than 0.75 second while skeletal muscle may have hours in which to recover from violent muscular exertion. Necessarily, therefore, cardiac muscle has a strongly developed mechanism for getting oxygen into the tissues. There is no sarcolemma around the muscle fibers which might impede the diffusion of

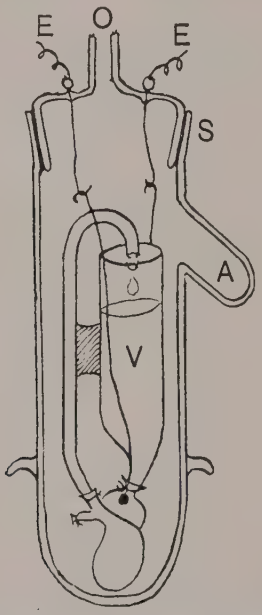


Fig. 291.—Modified vessel for Barcroft apparatus for measuring oxygen consumption of beating heart. *O*, connection to Barcroft manometer; *E*, electrodes; *A*, recess to hold sodium hydroxide for CO_2 absorption; *S*, joint to manometer. (From Clark and White: J. Physiol. **66**: 186, 1928.)

oxygen into the active tissue. There is a large capillary bed. Cobb[262] has calculated that cardiac muscle has 11,000 mm. of capillary length per c.mm. in contrast to 6,000 mm. of capillary length per c.mm. in active skeletal muscle. Cardiac muscle has a rich supply of muscle hemoglobin and cytochrome which also aid in its oxidative processes.

Methods.—In the study of metabolic activity of skeletal muscle, the standard procedure is to compare the chemical changes occurring in a stimulated muscle with those in a corresponding resting muscle. Unfortunately in the case of the heart, there is only one organ and that is rhythmically contracting. Therefore, it is very difficult to obtain the resting value of any chemical substance in the heart. Strips of ventricular muscle have been used, but their isolation involves considerable damage to the musculature. For these reasons,

cardiac metabolism is usually studied by analysis of the content of the material under consideration in the arterial and venous bloods and by the measurement of blood flow. These determinations give an accurate measure of the amount of material taken up by the heart but do not distinguish between storage and utilization. Special methods have been devised for the determination of the oxygen consumption of the heart. For small strips of tissue, or even for small hearts, the Warburg or Barcroft apparatus has been used (Fig. 291). For larger hearts, either the oxygen A-V difference is obtained, or the gaseous metabolism of a heart-lung preparation is determined. In the latter method a correction for the metabolism of the lungs which form a part of the biological system must be made.

Oxygen Utilization.—In any metabolic study, the first question to be solved is the amount of oxygen used, for this analysis gives a measure of the total metabolic activity. Numerous determinations of the oxygen consumption of the heart have been made, and the results have demonstrated that there are two chief factors which affect the amount used: the rate and the diastolic volume. In the frog's heart, Clark and White[259] observed that at the lower frequencies there was an increase of oxygen consumption proportional to the increase in rate but at the higher frequencies the total amount of oxygen used became less. In the dog's heart, Cohn and Steele[263] found that increasing the rate from 139 to 169 beats per minute changed the average oxygen consumption from 4.69 to 5.39 ml. per gram per hour. From these results and many others, it is obvious that an increase in rate affects oxygen consumption.

Increasing the diastolic volume also increases the oxygen consumption. Under these conditions the heart responds with a greater force of contraction (Starling's Law of the Heart, see page 346), and the additional force needs extra energy (Starling and Visscher,[274] Hemmingway and Fee[271]). Since the rate and the stroke output are the chief determining factors in the output of the heart, it becomes clear from these results that a change in cardiac output would demand a corresponding change in oxygen consumption.

Efficiency of the Heart.—The ratio between the output of energy by the heart and the input gives the efficiency of the heart as a pump. This factor has been determined by numerous observers using different formulas for the calculation of the output of work. All of these formulas contain two factors, the one involving the increase in pressure and the other depending on the movement of the column of blood. For example, the formula used by Evans[266] for calculating the work done by the heart is:

$$W = 7\left[\frac{QR}{6} + \frac{mV^2}{g}\right]$$

where W = work in kg. m.
Q = volume of blood in liters.
R = arterial pressure in m. of blood.
m = mass of blood in kg.
V = the mean velocity of blood at the aortic orifice during systole in m. per sec.
g = gravity constant = 9.8 m. per sec. per sec.

Regardless of the exact formula used, the results give an efficiency for cardiac muscle of the same order of magnitude as for skeletal muscle; i.e., from 10 to 25 per cent. The chief factor which affects efficiency is the amount of work which the heart does, because, when the output of work is low, the efficiency is also low. It increases with increasing amounts of work and then reaches a plateau. Additional amounts of work may even lower the efficiency. Visscher and his associates[265, 278] have been using the efficiency of the heart as a measure

of the activity of cardiac drugs. Their findings show that certain glucosides of digitalis have the ability to increase the mechanical efficiency of the failing heart.

Enzyme Systems of the Heart.—The heart muscle has a rich supply of muscle hemoglobin and cytochrome. Millikan[272] states that, as compared with other types of muscles, the hearts of large mammals have the most muscle hemoglobin, and that these hearts are characterized by having slow repetitive activity requiring the development of considerable force. The beef heart muscle is the favorite source of the biochemist for the isolation of cytochrome *c*. Since the oxygen consumption of the heart is decreased by cyanide, it may be concluded that the cytochrome-cytochrome oxidase system is involved in the activation and utilization of oxygen. Flavoprotein, the next component in the oxidative chain, is also present. In fact, Straub[276] has isolated a special heart flavoprotein which Corran, Green, and Straub[270] have shown to be active in the catalysis of the oxidation of DPN (coenzyme I) by methylene blue. The activity of this heart flavoprotein is such that one molecule will catalyze the oxidation of 8,500 molecules of DPN per minute. Numerous dehydrogenases are also present in heart muscle. The properties of lactate, malate, and β-hydroxybutyrate dehydrogenases from this source have been studied in detail by Green and his associates.[268-270] Succinate dehydrogenase (Stotz and Hastings[275]) is also present

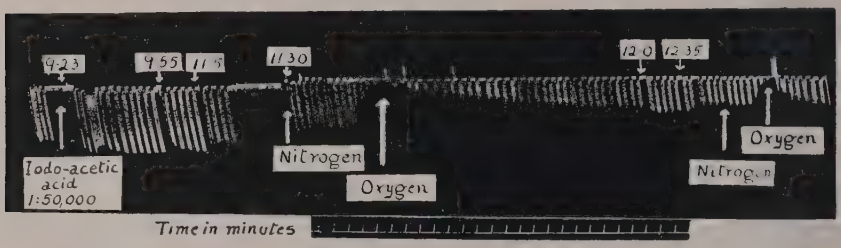


Fig. 292.—Effect of iodoacetate on frog's ventricle perfused under aerobic and anaerobic conditions. (From Clark, Eggleton, and Eggleton: J. Physiol. 75: 340, 1932.)

in considerable quantity. The heart is rich in DPN. It is quite obvious from the evidence at hand that heart muscle is well supplied with all the components of the oxidative systems as they are known at the present time.

Glycolysis of cardiac muscle as studied in enzymatic solutions proceeds along lines similar to those observed in skeletal muscle (Ochoa[273]).

Chemical Substances Used for Energy Production.—It has been known for a long time that glucose may be used by the contracting heart, the magnitude of the utilization depending on the amount of work that the heart does. Evans, Grande, and Hsu[267] found that the dog's heart uses an average of 70 mg. of glucose per 100 grams of heart muscle per hour working under normal arterial pressures. Wertherimer[280] and Visscher and Mulder[277] concluded that the utilization of glucose may not pass through a glycogen stage since they were unable to detect any decrease of glycogen in the heart working under aerobic conditions. Therefore, the utilization of blood glucose may be more direct than in the case of skeletal muscle. Under anaerobic conditions lactate is formed from glycogen. The fatigue level of lactate is much lower in cardiac muscle than in skeletal muscle: about 0.10 per cent for cardiac muscle in contrast to 0.30 per cent for skeletal. Under aerobic conditions, lactate may be

used by the heart (Evans et al.[267]). The heart muscle may also use pyruvate (Braun-Menendez, Chute and Gregory[257]) and β-hydroxybutyrate (Walters, Fletcher and Mirsky;[279] and Barnes et al.[256]). Claims have also been made that the isolated heart may use amino acids, but these views are based rather on calculations than on direct evidence (Clark, Gaddie and Stewart[260]).

A correlation of these numerous findings has been made by Clark and his associates[261] who studied the frog's heart by the aid of the inhibitory activity of monoiodoacetate. In the presence of oxygen, this substance does not change the capacity of the heart for work. In nitrogen, however, the ability of the heart to work is decreased when monoiodoacetate is present (Fig. 292). Since monoiodoacetate inhibits the breakdown of glycogen to lactate, it may be inferred from these results that this cycle plays no role under aerobic conditions but has an important emergency function under anaerobiosis. The mammalian heart is slightly affected by this poison even under aerobic conditions, and the activity of the heart may be restored by the addition of lactate, pyruvate, phosphoglycerate or propionate (Chang[258]). Under anaerobic conditions, phosphocreatine and adenylpyrophosphate are broken down in the heart.

Summary.—Though it is difficult to coordinate all of these findings, the following summary may be an aid. Oxidation of glucose is the normal source of energy for the heart. When the glucose content of the blood is low, β-hydroxybutyrate produced from fat in the liver may be used. Pyruvate and lactate may also be metabolized and may aid in giving energy to the heart during muscular exercise. Glycogen stores may be used during anoxia in the cardiac muscle. Thus the glycogen-lactate mechanism may be an emergency device for supplying energy under low oxygen concentrations or during temporary blocking of the coronary circulation. Amino acids are probably used following preliminary deaminization in the liver. The main source of energy for cardiac muscle is glucose.

CHAPTER LIII

GENERAL PROTEIN METABOLISM

A protein may be defined as a naturally occurring substance of high molecular weight which is composed of amino acid groups united together by an amide type of linkage. Since the animal body is unable to build proteins from inorganic substances and since proteins are being used continually in metabolism, they must be supplied from outside sources. It is also necessary to consider the chemical nature of the protein as well as the energy content since different proteins are not utilized to the same extent by the animal.

THE CHEMICAL NATURE OF PROTEINS

The predominant linkage in proteins is the so-called peptide linkage, the combination of the amino group of one amino acid with the carboxyl group of another. For example, the reaction between alanine and glycine to form the dipeptide, alanylglycine, is,

$$\underset{\text{alanine}}{CH_3CHNH_2CO\overset{\cdot\cdot}{O}H} + \underset{\text{glycine}}{H\overset{\cdot\cdot}{N}HCH_2COOH} \rightarrow \underset{\text{alanylglycine}}{CH_3CHNH_2CONHCH_2COOH} + H_2O.$$

Since the dipeptide contains a free amino group and a free carboxyl group, it is capable of combining with two more amino acids. This process may be continued until a chain of amino acids of indefinite length is formed.

The evidence in favor of the peptide type of linkage in the protein molecule has been summarized by Vickery and Osborne[350] as follows:

1. The peptide linkage accounts for the large amount of free amino nitrogen in the end products of protein hydrolysis which is not present in the native protein.

2. The biuret reaction, characteristic of proteins and proteoses, is given by compounds containing the peptide bond.

3. The synthetic polypeptides obtained by Fisher from the naturally occurring isomers of amino acids are hydrolyzed by some of the enzymes of the digestive tract.

4. Polypeptides have been found among the products of incomplete hydrolysis of proteins.

5. During the hydrolysis of proteins amino and carboxyl groups are liberated at an equal rate.

Although the evidence for the peptide linkage is very strong, there are various peculiarities in the behavior of proteins that cannot be explained on the basis of a large polypeptide molecule. The polypeptide theory does not explain denaturation of the molecule by alcohol or heat. Pepsin, the proteolytic enzyme of the gastric juice, does not liberate amino acids; it does not act on polypeptides nor on synthetically formed products of amino acids. The insolubility in water of many proteins cannot be predicted from the polypeptide theory. In order to explain these deviations from the usually accepted theory, numerous other hypotheses have been suggested. Sørensen,[340] for example, believes that proteins are made up of different components in dynamic equilibrium. Under certain conditions these components will combine in a definite manner,

and the separation of crystals may represent one combination while precipitation by salt may result in an entirely different one. Wrinch,[358] on the other hand, has developed the theory of a cycloid structure of the protein molecule. Bergmann and Niemann[297] have put forth the interesting idea that proteins consist of groups of units, each unit being composed of 288 amino acids arranged in recurring sequence. Regardless of the exact structure of any protein, amino acids must be regarded as the building stones in its formation, and they form the basis of protein metabolism.

The reactions that amino acids possess in common are due to the end groups containing the carboxyl and amino radicals, whereas the characteristic reactions of each of the amino acids depend on the chemical differences in the radicals attached to the end groups. The amino acids, with two exceptions, are α-amino acids. The exceptions are proline and hydroxyproline which are cyclic compounds and possess an α-imino group.

PROTEIN STARVATION

The first step in the study of protein metabolism is to determine the magnitude of the chemical breakdown in the tissues when no food is given; i.e., the endogenous protein metabolism. During the first few days of a fast, the amount of protein metabolized depends upon the glycogen content of the individual and the quantity of protein ingested before the starvation began. After an initial rapid decrease, there is a slow diminution of the nitrogen output. In the subject studied by Benedict[295] the total nitrogen eliminated on the last day of food was 11.54 grams and on the thirty-first day of the fast was 6.94 grams. Lusk[60] has calculated that the subject of Benedict's study lost 277 grams of nitrogen from his body or 16 per cent of the total amount present at the beginning of the fast. Junkersdorf and Lisenfeld[317] obtained much lower values in two subjects after a long period of starvation. In one subject, after a fast of 39 days, the output of urinary nitrogen was 4.81 grams per day. In the other subject this value had decreased to 3.32 grams on the thirty-eighth day of starvation.

Lower values of nitrogen output are obtained by feeding a subject a diet very low in protein but containing sufficient fat and carbohydrate to supply the necessary Calories. Mitchell and Hamilton,[284] summarizing values obtained on human subjects, reported variations from 3.8 to 1.75 grams of nitrogen per day. The amount of protein metabolized under these conditions has been termed the *minimum protein catabolism.* It represents the protein used in the wear and tear of the organs of the body and lost through the secretion of

TABLE LXVIII

LOSS OF WEIGHT OF ORGANS DURING A FAST (VOIT[354])

ORGAN	PERCENTAGE LOSS IN WEIGHT OF FAT-FREE TISSUE
Skeleton	5
Muscles	42
Heart	16
Brain and cord	22
Spleen	57
Liver	50
Pancreas	62
Lungs	29

the digestive juices. A rough estimate of the loss of protein may be obtained by studying the loss in weight of various organs of the body during starvation. Voit[354] calculated this loss in the organ of a dog before and after a twenty-four-day fast (Table LXVIII).

Voit's findings suggest that there is a greater mobilization of protein from glands and skeletal muscle than from the heart and brain. It appears that during starvation the most vital organs live at the expense of those whose functions are not so necessary for life. Another observation showing that there is a transfer of nitrogenous substances from organ to organ in the body is the fact that the amino nitrogen of the blood does not decrease during prolonged fasting (Van Slyke and Meyer[349]).

NITROGEN EQUILIBRIUM

The next step in the study of protein metabolism is the determination of the quantity of protein which it is necessary to take in daily to balance the nitrogen lost in the excreta. One might expect that feeding an amount of protein which corresponds to the minimum protein catabolism would balance the output of nitrogen. This is not the case, as Voit and Korkunoff[355] demonstrated by feeding a dog meat from which most of the nitrogenous substances other than protein had been removed. Their results are given in Table LXIX.

TABLE LXIX

ESTABLISHMENT OF NITROGEN EQUILIBRIUM IN A DOG AFTER STARVATION
(VOIT AND KORKUNOFF[355])

FOOD	N IN FOOD	N IN EXCRETA	DIFFERENCE
Starvation	0	3.996	−3.996
100 grams meat	4.10	5.558	−1.458
140 grams meat	5.74	6.495	−0.755
165 grams meat	6.77	7.217	−0.447
185 grams meat	7.59	7.804	−0.214
200 grams meat	8.20	8.726	−0.526
230 grams meat	10.24	10.579	−0.339
360 grams meat	11.99	12.052	−0.062
410 grams meat	15.58	14.314	+1.266
360 grams meat	13.68	13.622	+0.058
Starvation 3rd day	0	4.026	−4.026

These experiments showed clearly that nitrogen equilibrium is reached only by feeding from three to four times the amount of protein that is metabolized during starvation.

A tremendous amount of work has been done in recent years to establish the amount of protein in the food necessary for the maintenance of nitrogen equilibrium in man. Experiments directed toward this end must be carried out over long periods of time, for nitrogen equilibrium is affected by previous protein ingestion. When a subject passes from a high to a low level, equilibrium is reestablished only after a long delay. Some of the protein already present in the tissues is metabolized and the amount of this is dependent on the previous diet. Borsook and Keighley[304] have termed the metabolism of the protein left from former ingestion the "continuing nitrogen metabolism" to distinguish it from the exogenous and the endogenous breakdown of protein. In a review of the data obtained from various sources Sherman[348] reports that nitrogen equilibrium is obtained by the daily ingestion of from 21 to 65 grams of protein,

the average being 44.4 grams. From his experiments on feeding bread and other grain products he found that 35 grams of protein from these sources are sufficient for actual maintenance requirements. To provide a margin of safety, he recommends 70 grams of protein a day. The lower level, the amount of protein that is just sufficient for the needs of the body, is called the *physiological protein minimum*. The amount that must be taken to insure an adequate supply is termed the *hygienic protein minimum* (Luck[42]). The average diet of man under normal conditions has sufficient protein to supply his needs. The diet of the United States soldier contains 131 grams of protein. The inhabitants of large cities ingest about 100 grams per person and hospital diets contain about the same amount. Since the various body tissues are made up of different proteins, a large variety of amino acids is necessary for the synthetic processes that occur in the formation of body proteins. Man has adjusted himself to this need by taking an excess of protein in his diet.

There are several factors which influence the level at which nitrogen equilibrium is established. If carbohydrate or fat is ingested with protein, the amount of protein needed for equilibrium is less than the amount necessary when protein is the only ingredient in the diet. Voit and Korkunoff[355] found that for every 100 grams of protein metabolized in starvation, 368 grams of protein alone, 157 to 193 grams of protein with fat or 108 to 134 grams of protein with carbohydrate had to be consumed in order to prevent loss of nitrogen to the body. Because of this fact the name "protein sparers" has been given fats and carbohydrates. Since such large amounts must be ingested to obtain the proper caloric value, it is practically impossible for man to subsist on protein alone. A subject fed on lean meat exclusively would be starved because he would oxidize his body stores of fat and carbohydrate in order to get the necessary calories. This fact forms the basis of treating obesity by diet.

Another factor in the maintenance of nitrogen equilibrium is the type of protein ingested. The tissues require an adequate supply of protein for their daily needs, but it is difficult to measure exactly this demand inasmuch as different tissues require different groups of amino acids for building their special proteins. The body may be forced to discard a large number of amino acids from a protein in order to obtain a sufficient amount of an individual acid. Thomas[344] determined the biological value of proteins from various sources by determining the amount of ingested protein required to balance the minimal nitrogen output. His results were as follows:

TABLE LXX

RELATIVE VALUE OF PROTEINS AS FOOD MATERIALS (FROM THOMAS[344])

SOURCE	PERCENTAGE UTILIZATION
Ox flesh	104.7
Milk	99.7
Fish	94.5
Rice	88.3
Cauliflower	85.8
Potato	78.9
Spinach	63.8
Flour	39.6

The results are given in terms of the amount of tissue protein spared by the ingestion of 100 grams of protein from the various sources. The high value for ox flesh, 104.7 per cent, may signify that other nitrogenous sub-

stances besides protein play an important role in metabolism. From the work of Thomas it would appear that protein from animal sources is far superior to that from vegetables. Other observers, however, have not obtained evidence of such marked differences between animal and vegetable protein. Hindhele[315] showed that nitrogen equilibrium may be obtained on a diet of potatoes which yields 25 grams or less of protein daily. Sherman reported that human

Fig. 293.—Photographs of rats of same brood on perfect diet (uppermost picture); on a maintenance diet but inadequate for growth (middle picture); and on a diet that was inadequate both for maintenance and growth. (From Mendel and Osborne.)

subjects can be kept in nitrogen equilibrium on diets of corn and oatmeal with 10 per cent milk protein. Such a diet furnishes only about 35 grams of protein per day. These values compare very favorably with similar experiments on nitrogen equilibrium in which the source of protein was of animal origin.

The variations in the ability of proteins to maintain the body in nitrogen equilibrium may be due to differences in chemical structure. For example, if

an animal is fed gelatin it metabolizes this substance completely and, in addition, uses some of the protein of its body. Gelatin, a derivative of collagen, does not contain tyrosine, cystine or tryptophane in appreciable amounts. When these amino acids are added to the gelatin, nitrogen equilibrium may be established (Kaufman[318]). Other proteins, such as gliadin and zein, are also deficient in certain amino acids (Table LXXI). These facts led to a determination of the indispensable amino acids without which growth is impossible. The experiments designed for this study consisted in feeding rats a diet to which mixtures of amino acids or various proteins were added. Using a diet in which zein was the sole source of protein, Willcock and Hopkins[357] observed that the rats lost

TABLE LXXI

THE AMINO ACID CONTENT (GRAMS PER CENT) OF A NUMBER OF PROTEINS, DETERMINED MAINLY BY ISOLATION METHODS (MITCHELL AND HAMILTON[284])

AMINO	GELATIN	CASEIN	LACT-ALBUMIN	GLIADIN	ZEIN	EDESTIN
Glycine	25.5	0.4	0.4	0.0	0.0	3.8
Alanine	8.7	1.8	2.4	2.0	9.8	3.6
Valine	0.0	7.9	3.3	3.3	1.9	+
Leucine-isoleucine	7.1	9.7	14.0	6.6	25.0	20.9
Aspartic acid	3.4	4.1	9.3	0.8	1.8	10.2
Glutamic acid	5.8	21.8	12.9	43.7	31.3	19.2
Hydroxyglutamic acid	0.0	10.5	10.0	2.4	2.5	—
Serine	0.4	0.5	1.8	0.1	1.0	0.3
Proline	9.5	8.0	3.8	13.2	9.0	4.1
Hydroxyproline	14.1	0.2	—	—	0.0	2.0
Phenylalanine	1.4	3.9	1.2	2.3	7.6	3.1
Tyrosine	0.01	6.5	1.9	3.1	5.9	4.5
Cystine	0.17	0.3	4.0	2.4	0.8	1.0
Arginine	9.1	5.2	3.0	3.2	1.8	15.8
Histidine	0.9	2.6	1.5	2.1	1.2	2.1
Lysine	5.9	7.6	8.4	0.6	0.0	2.2
Tryptophane	0.0	2.2	2.7	0.8	0.17	1.5
(Ammonia)	0.4	1.6	1.3	5.2	3.6	2.3
Total	92.4	94.8	81.9	91.8	103.4	96.6

TABLE LXXII

EXPERIMENTAL DIETS USED IN THE STUDY OF AMINO ACIDS NECESSARY FOR NUTRITION AND GROWTH (OSBORNE AND MENDEL[335])

FOOD MATERIAL	DIET			
	I	II	III	IV
	Gm.	Gm.	Gm.	Gm.
Zein	18.00	17.46	16.92	13.50
Protein-free milk	28.00	28.00	28.00	28.00
Starch	27.00	27.00	27.00	27.30
Butter fat; lard	27.00	27.00	27.00	26.70
Water	15.00	15.00	15.00	12.00
Tryptophane		0.54	0.54	
Lysine			0.54	
Lactalbumin				4.5
Results { growth	−	−	+	+
Results { maintenance	−	+	+	+

weight rapidly. When tryptophane was added to the diet the loss in weight was stopped but there was no growth (Fig. 293). In order to produce a gain in weight both tryptophane and lysine had to be added (Osborne and Mendel[335]). It was not necessary to give the missing amino acids in pure form since feeding

a diet containing protein with adequate amounts of lysine and tryptophan in the molecule produced the same effect. A graphic summary of this work is given in Figs. 294 and 295 and the diets used are given in Table LXXII.

The latest discovery in this field was made by Rose and his associates.[285] They fed rats nineteen pure amino acids in the same percentages that they

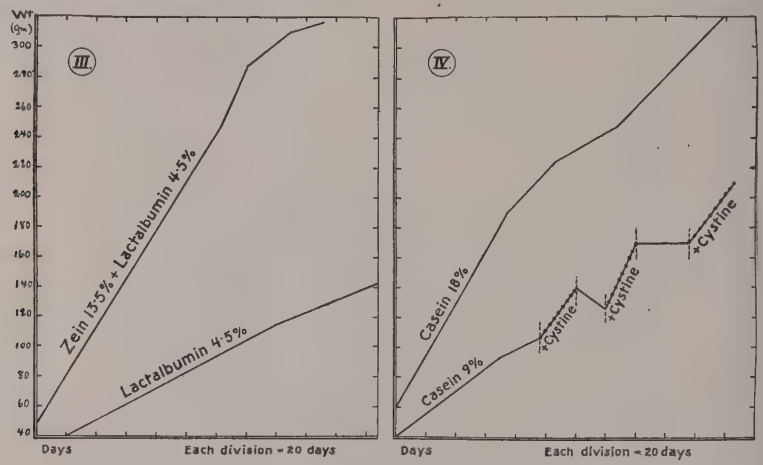


Fig. 294.—Curves of growth of rats on basal rations plus the proteins indicated. In curve III the effect of the addition of zein to an inadequate allowance of the perfect protein, lactalbumin, is shown; and in IV the effect of the addition of cystine to a deficient casein allowance. (From Lafayette B. Mendel and T. B. Osborne.)

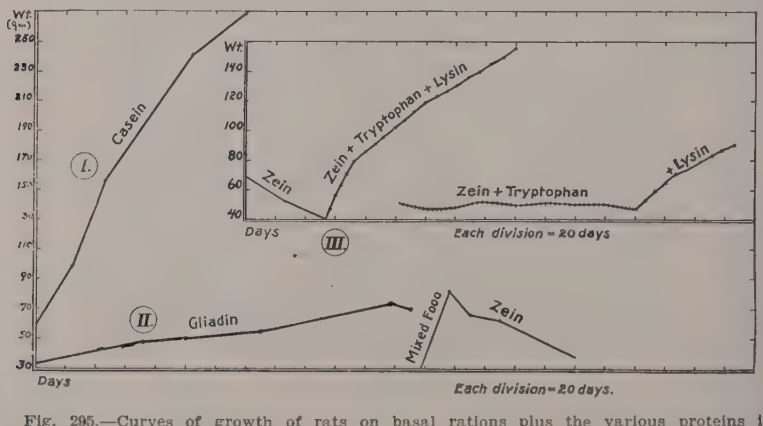


Fig. 295.—Curves of growth of rats on basal rations plus the various proteins indicated. The normal curve may be taken as that with casein (*I*). Adapted from Lafayette B. Mendel and T. B. Osborne.)

occur in casein. On this amino acid diet the rats lost weight but recovered it if 5 per cent casein, gliadin or gelatin was added. This result suggested that there was an unknown growth-promoting substance in the protein that was not present in the pure amino acids. Their search for this unknown compound resulted in the discovery of a new amino acid essential for growth, α-amino-β-

hydroxy-n-butyric acid, to which they gave the name "threonine." The synthetic compound prepared by Carter[308] has the same growth-producing power as the naturally occurring product. This discovery makes it possible for the first time to raise animals on purified amino acids and to determine experimentally the exact physiological importance of each acid by eliminating it

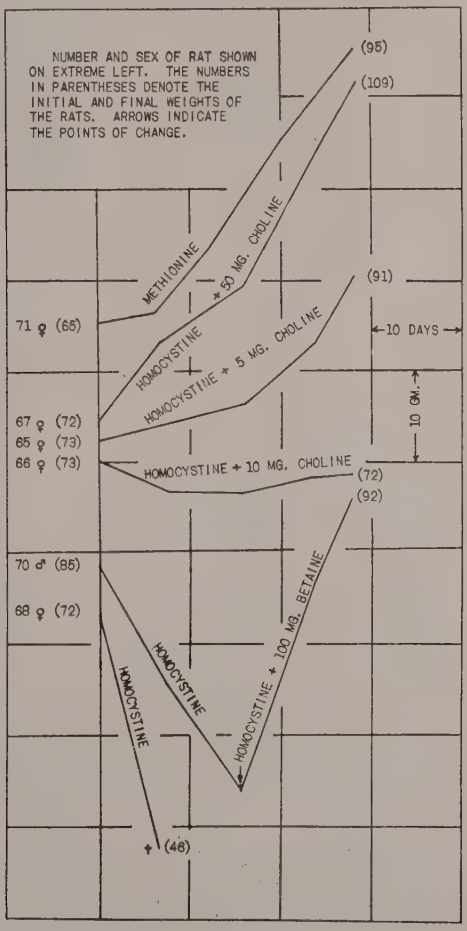


Fig. 296.—The effect of feeding homocystine, choline, and methionine on the growth of rats. (From du Vigneaud, et al.: J. Biol. Chem. 131: 57, 1939.)

from the diet. One of the difficulties in experiments of this type is that small traces of other amino acids may contaminate those of the essential group. Therefore, the use of only highly purified amino acids can give the final answer to this problem. The classification of the amino acids with respect to their growth effects is given in Table LXXIII.

TABLE LXXIII

FINAL CLASSIFICATION OF THE AMINO ACIDS WITH RESPECT TO THEIR GROWTH EFFECTS (ROSE[285])

INDISPENSABLE	DISPENSABLE
Lysine	Glycine
Tryptophane	Alanine
Histidine	Serine
Phenylalanine	Norleucine
Leucine	Aspartic acid
Isoleucine	Glutamic acid
Threonine	Hydroxyglutamic acid
Methionine	Proline
Valine	Hydroxyproline
Arginine	Citrulline
	Tyrosine
	Cystine

It is interesting to note that of the ten indispensable amino acids, both the d- and l- forms of tryptophane, histidine, phenylalanine, and methionine may promote growth, but only the natural or l-form of valine, leucine, isoleucine, lysine, and threonine have this function.

Another interesting fact is that homocystine cannot replace methionine. The livers of animals on a diet of homocystine were found to be fatty. On giving choline with homocystine, du Vigneaud and his associates[351, 352] found that not only were the livers free of fat, but the growth rate was normal; whereas on a diet of either homocystine or choline alone, growth was retarded (Fig. 296). These results demonstrate that choline is not only essential for the removal of fat from the liver (see Chapter LV), but also that it aids in the conversion of homocystine to methionine by its ability to act as a methylating donator. Both choline and methionine are lipotropic agents (see Chapter LV).

THE SPECIFIC DYNAMIC ACTION OF PROTEIN

After the ingestion of protein there is an increase in basal metabolism which amounts to about 30 per cent of the caloric value of the protein. This stimulating action of protein on metabolism is called its specific dynamic action. The fact that amino acids injected into the blood stream have an effect which is almost equal to that obtained by ingestion of an equivalent amount of protein shows that intestinal movements and the processes of digestion and absorption play a very minor part in raising the metabolism. Specific dynamic action is associated with changes in the amino acids in the liver, for Mann and his colleagues[329] have shown that there is no change in metabolism when the acids are injected into hepatectomized dogs. The extra heat production is associated with deaminization and urea formation and not with the complete combustion of the amino acids. Lusk observed a high specific dynamic action of amino acids in phlorizinized dogs in which, because of the action of the drug, part of the amino acid molecule is converted into glucose and lost in the urine. Not all the amino acids have the same specific dynamic action; for example, valine and histidine have none, while phenylalanine and tyrosine have a greater activity than alanine and glycine.

CHAPTER LIV

SPECIAL METABOLISM OF PROTEINS

The special metabolism of proteins involves the intermediate changes which take place between the ingestion of the protein molecule and the formation of the end products which are excreted. Some of these changes occur in the digestive tract and are due to the activity of the digestive enzymes (see Chapter LXVI).

Pepsin, the gastric protease, produces a slow and incomplete protein hydrolysis. The main products of the action of this enzyme are proteoses and peptones. The initial breaking of the protein molecule into shorter chains enables the intestinal enzymes to continue the fragmentation. The exact point of cleavage of the protein molecule in gastric digestion is not known. Torbet and Bradley[345] have presented evidence that the enzymatic activity may involve tyrosine. The amount of reactive tyrosine in casein is so small that it is impossible to estimate it with any degree of accuracy. However, after pepsin has acted on this protein, a markedly positive test is obtained. This fact indicates that tyrosine is converted into a reactive form by the action of pepsin. Practically no absorption of the split products of protein digestion occurs in the stomach.

The next step in the digestion of proteins occurs in the small intestine through the action of trypsin, an enzyme secreted by the pancreas, and erepsin, an enzyme produced by the small intestine itself. These enzymes rapidly liberate amino acids from the products of gastric digestion and the amino acids pass from the lumen of the intestine into the blood stream. There is some evidence that small amounts of proteins may pass through the intestinal wall. Wells[356] having fed a series of guinea pigs a diet of egg proteins, observed that these animals gave strong anaphylactic reactions when injected with egg albumen between the thirtieth and sixtieth days of feeding, but later showed only slight responses. He concluded that daily absorption of protein from the food rendered these animals hypersensitive to that protein with a subsequent development of immunity. Small amounts of polypeptides may also pass through the intestinal wall, for London and Kotschneff[325] have observed an increase in these compounds in the portal blood following ingestion of casein.

AMINO ACIDS IN BLOOD AND TISSUES

Although small amounts of proteins and polypeptides may pass through the intestinal wall, the chief products of protein digestion found in the portal blood are the amino acids. The evidence that free amino acids are present in the blood has been obtained by various modes of investigation. Abderhalden,[287] using large amounts of blood, was able to isolate and identify amino acids. Abel, Rowntree and Turner[290] developed an ingenious method for removing diffusible substances from the circulating blood by dialysis. This method, known as vividiffusion, consists in connecting the two ends of a cut artery of an anesthetized animal to a long collodion tube. The tube, coiled many times, is in an isotonic salt solution. As the blood passes through the tube, the diffusible constituents of the plasma pass into the surrounding fluid. In experiments it is possible to recover several of the amino acids from the salt solution, thus demonstrating that they are present free in the blood stream.

The methods of isolation and dialysis have shown that amino acids do occur in the blood. In order to follow the changes in these constituents, it is necessary to use quantitative methods. Levene and Van Slyke[323] developed a method for the determination of amino

nitrogen in the urine based on the fact that nitrous acid reacts with amino acids to liberate nitrogen gas according to the equation:

$$RNH_2 + HNO_2 = ROH + H_2O + N_2$$

This method has been employed also in blood studies. The most recent modification is one in which this reaction is adapted for use with the manometric method (Van Slyke[346]). The normal value for amino nitrogen in the blood varies from 5 to 8 mg. per 100 ml. of blood. This value is not affected by starvation, but does increase slightly after the ingestion of protein. Folin and Berglund[311] showed that in man the ingestion of 135 grams of gelatin increased the amino nitrogen from 6.7 mg. to 11.7 mg. per 100 ml. of blood.

Free amino acids are present also in the tissues. Van Slyke and Meyer[347] injected solutions of amino acids into animals and studied the disappearance of these acids from the blood and their accumulation in the tissues. They found that the amino acids are absorbed by the tissues without undergoing any immediate change. The greatest absorption occurs in the liver. The results of one of their experiments are given in Table LXXIV. Although the disappear-

TABLE LXXIV

EFFECT OF INJECTING 3.39 GRAMS OF AMINO NITROGEN INTO A DOG WEIGHING 7.4 KILOGRAMS (VAN SLYKE AND MEYER[347])

TISSUE	MG. AMINO NITROGEN PER 100 GRAMS TISSUE	
	BEFORE INJECTION	AFTER INJECTION
Liver	48	127
Muscle	46	78
Kidney	52	111
Blood	5.8	31.5

ance of the amino acids from the blood is rapid, it is never complete, for the blood contains these substances even during starvation. There are, therefore, two sources of the amino acids in the blood, the digested food proteins and the hydrolyzed tissue proteins. The concentration of amino acids is greater in the tissues than in the blood (Table LXXV). Van Slyke and Meyer suggest that this difference may be due either to mechanical adsorption or to the formation of loose molecular compounds between the amino acids and the tissue proteins.

THE FATE OF THE AMINO ACIDS

After the above study, Van Slyke and Meyer[349] determined the length of time the amino acids remain in various organs. Their results are given in Table LXXV.

TABLE LXXV

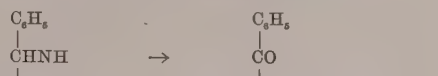
EFFECT OF INJECTING 2.70 GRAMS AMINO NITROGEN INTO A DOG WEIGHING 10.3 KILOGRAMS (VAN SLYKE AND MEYER[349])

TISSUE	AMINO ACIDS, MG. PER 100 GRAMS TISSUE		
	BEFORE	1 HR. AFTER	3 HR. AFTER
Muscle	47	68	67
Liver	–	79	34
Blood	8.2	18.3	12.4

Organs such as kidney, intestine, pancreas and spleen, gave results similar to those obtained on muscle. It was only in the liver that a rapid disappearance of amino acids occurred and this was associated with an increase in blood urea.

Studies of the blood and urine changes which occur in animals deprived of the liver have given additional evidence that this organ is the chief site of the metabolic changes undergone by the amino acids. Mann and his associates[329] have succeeded in keeping dogs alive for many hours in good condition following the extirpation of the liver. Amino acids accumulate and urea diminishes in the blood of these animals.

The Process of Deaminization.—The experiments of Van Slyke and of Mann and their associates have demonstrated conclusively that amino acids undergo metabolic changes in the liver. The main change is a process of deaminization, a splitting off of ammonia. It is agreed generally at the present time that this is an oxidative process. Neubauer[334] fed phenyl glycine to a dog and recovered phenylglyoxylic acid in the urine:



On the basis of this experiment and others, he concluded that amino acids are converted into the corresponding keto acids by an oxidative process which occurs according to the following equation:

$$RCHNH_2COOH + \tfrac{1}{2}\ O_2 \rightarrow RCOCOOH + NH_3.$$

The most recent evidence that the process of deaminization is an oxidative one has been obtained from a study of the oxygen uptake and ammonia production following the addition of amino acids to tissue slices. Krebs[320] observed that alanine added to liver and kidney tissue increases the production of ammonia and the consumption of oxygen. Negative results were obtained with other tissues. Later, Krebs[321] isolated two enzyme systems from the liver, one which deaminizes the dextro form and the other the levo form of the amino acids. Bernheim and Bernheim,[398] after isolating the enzymes which oxidize amino acids, found that one atom of oxygen is taken up for every molecule of amino acid oxidized. These results, obtained by different investigators with various techniques, show that the chief process is oxidative, although they do not eliminate the possibility that other types of deaminization take place in the liver. It is interesting to note that conclusive evidence that the kidney is able to deaminize amino acids was obtained only after the introduction of the tissue slice method into metabolic experimentation.

Another interesting mechanism for deaminization is the transfer of amino groups to keto acids discovered by Braunstein and Kritzmann.[307] They showed that a reversible reaction takes place according to the following equation:

glutamic acid + pyruvic acid = α-ketoglutaric acid + l-alanine.

Amino acids give up readily their amino group to a ketoglutaric acid to form glutamic acid. This reaction forms a possible link between protein and carbohydrate metabolism, and explains how some of the dispensable amino acids may be formed. It also demonstrates the possibility of a rapid interchange of amino nitrogen. Direct proof of this interchange has been supplied by Schoenheimer and his associates. By feeding tyrosine containing heavy nitrogen, N^{15}, they showed that ten days later heavy nitrogen was contained in the monoaminodicarboxylic acids, in arginine, and in histidine. With this same tag,

they also demonstrated that heavy nitrogen in ingested ammonium citrate soon finds its way into amino acids, demonstrating that ammonia enters into the synthetic formation of these acids.

Oxidation of Keto Acids.—One of the end products of oxidative deamination is a keto acid which the animal is capable of handling by oxidation or conversion to sugar. Keto acids are oxidized readily to carbon dioxide and water. It is supposed that this process occurs by oxidation of the α-carbon to a carboxyl group. Following the liberation of carbon dioxide from this molecule, a fatty acid is formed. The fatty acid is oxidized according to the usual pathways for the breakdown of these substances (see Chapter LV).

The reactions are as follows:

$$RCH_2CHNH_2COOH + \tfrac{1}{2}\ O_2 \rightarrow RCH_2COCOOH + NH_3$$
$$RCH_2COCOOH + \tfrac{1}{2}\ O_2 \rightarrow RCH_2COOH + CO_2$$
$$RCH_2COOH + nO_2 \rightarrow xCO_2 + yH_2O$$

Keto acids such as pyruvic may also be converted into lactic acid.

Conversion of Amino Acids Into Sugar.—The animal body is able to convert some of the amino acids into sugar. This process has been studied by feeding the acids to an animal made diabetic by the removal of the pancreas or by injection of phlorizin. Dakin[309] has summarized the results of experiments of this type as follows:

1. The amino acids which yield glucose freely in the diabetic organism are all those, except valeric, which contain two, three, four or five carbon atoms.

2. Arginine is the only amino acid with more than five carbon atoms which may furnish glucose freely.

3. All the straight chain amino acids except lysine yield sugar.

4. The amino acids with branched chains, including valine, leucine and isoleucine, furnish little or no sugar.

5. Proline is the only cyclic amino acid known to yield glucose.

The exact mechanisms involved in the conversion are not known. The fact that simple keto acids, such as pyruvic, formed in the process of deamination are converted readily into glucose in the animal body may be of significance in this connection.

Conversion Into Fat.—The process of partial oxidation following deamination gives a fatty acid. This suggests the possibility that amino acids may play a role in fat storage. Experimental evidence for this conversion is not as convincing as that for the transformation of amino acids into glucose. Addis, MacKay and MacKay[291] found very little deposition of fat in rats fed a high protein diet. Indirect evidence for conversion has been obtained from a study of the respiratory exchange during the feeding of high protein diets. Atkinson, Rapport and Lusk[293] determined the respiratory quotient and the retention of carbon in dogs following the ingestion of large amounts of meat. They calculated that if all the retained protein carbon were deposited in the form of glucose the heat production would be greater than that actually observed. Therefore it must have been deposited as fat or as a mixture of fat and carbohydrate. The nonprotein respiratory quotients found in these experiments indicated that protein was being converted into fat. If all the assumptions made

by these authors are accepted, their experiments do indicate a transformation of protein into fat under conditions of excessive feeding of proteins. More direct evidence is needed on this point.

Synthesis of Proteins.—Amino acids are utilized in the building of proteins. During pregnancy and growth additional proteins are formed from the amino acids taken from the blood. During lactation large amounts of milk proteins are formed. These proteins must come from the amino acids transported by the blood. The exact mechanism of protein synthesis is very obscure. Alcock,[292] in a review of the scanty evidence bearing on this subject, suggests that the amino acids are taken up by the tissues and then broken down into a common unit which provides the basis for the synthesis of protein. After the construction of this basic molecule, the protein molecule is differentiated by the addition of other molecules. The exact nature of the final product is dependent on the tissue in which the protein is formed.

It may be that the liver or intestines change the amino acids which pass through these organs on their way to the tissues. The following facts point to a dominant control by the liver over the escape of amino acids into the blood stream. London and his associates[324] have found an increase in polypeptides in the blood coming from the liver during protein digestion. Injection of tryptophan into rats on a diet deficient in this substance does not improve the condition of these animals (Alcock[292]). Seth and Luck[337] found that after absorption from the intestine glutamic and aspartic acids do not produce a rise in blood amino nitrogen, while glycine and alanine give pronounced changes. Concerning the mechanism of this control and the liberation of amino acids in time of need, there is no available information at the present time.

THE END PRODUCTS OF PROTEIN METABOLISM

Analysis of the nonprotein nitrogen of the blood shows that it is chiefly derived from urea, amino acids, uric acid, creatine, creatinine, and a residue which is designated the "undetermined nitrogen." The quantity of nonprotein nitrogen of the whole blood of normal individuals averages 35 mg. per 100 ml., the nitrogen of urea accounting for one-half of the total. Wu[359] has investigated the partition of these substances between the corpuscles and plasma and his results are given in Table LXXVI.

TABLE LXXVI

NONPROTEIN NITROGEN SUBSTANCES IN PLASMA AND CORPUSCLES (From Wu[359])

	AVERAGE VALUES (MG. PER 100 ML.)	
	CORPUSCLES	PLASMA
Total Nonprotein N	49.3	28.80
Urea N	17.1	19.30
Uric Acid	1.93	3.92
Total Creatinine	8.32	1.47
Preformed Creatinine	2.48	1.24
Amino Acid N	9.47	5.52

In the urine, urea nitrogen may account for 80 per cent of the total nitrogen although the value varies with the amount of protein in the diet. Smith[339] has described the distribution of the nitrogenous compounds in the

urine of a man on a normal diet and compared it with that of the same individual after he had been on a low protein diet. His findings are given in Table LXXVII.

TABLE LXXVII

NITROGENOUS SUBSTANCES (GRAMS PER DAY) IN URINE OF MAN ON NORMAL AND LOW PROTEIN DIET (From Smith[339])

	NORMAL DIET	LOW PROTEIN DIET	
		AFTER 16 DAYS	AFTER 25 DAYS
	Gm.	Gm.	Gm.
Total N	9.32	2.37	1.58
Urea N	7.62	1.08	0.35
Ammonia N	0.41	0.31	0.23
Creatinine N	0.63	0.56	0.56
Uric Acid N	0.11	0.10	0.11
Undetermined N	0.55	0.32	0.33
Total Sulfur	0.61	0.24	0.19
Volume of urine (ml.)	1425	415	970

These results illustrate several important facts in connection with protein metabolism:

1. The total amounts of nitrogen and of all the nitrogenous metabolites, except creatinine, diminish during partial protein starvation.

2. The output of urea decreases relatively more than the output of total nitrogen. Therefore the relative amounts of the other nitrogenous metabolites increase.

3. The output of creatinine is unchanged.

4. The total amount of urine diminishes. This fact demonstrates that the end products of protein metabolism exert a diuretic action.

Urea.—The high concentration of urea in the blood and urine suggests that this substance is the chief end product of protein metabolism. Chemically, urea [$CO(NH_2)_2$] is a diamide of carbonic acid, having 46.6 per cent nitrogen in the molecule. In the preceding chapter evidence was presented that deamination of the amino acids occurs in the liver with production of urea. Krebs and Henseleit[322] have proposed an attractive theory for the conversion of ammonia to urea in this organ. They showed that the addition of ornithine or citrulline to liver slices increases the formation of urea, especially in the presence of ammonia. The concentration of ornithine did not change but the amount of citrulline decreased. From these and other observations Krebs and Henseleit concluded that ammonia is converted to urea through the following reactions:

1. $RCH_2NH_2 + CO_2 + NH_3 \rightarrow RCH_2NHCONH_2 + H_2O$ [R = $CH_2CH_2CHNH_2COOH$]
   ornithine citrulline

2. $RCH_2NHCONH_2 + NH_3 \rightarrow RCH_2NH.C(:NH)NH_2 + H_2O$
   citrulline arginine

3. $RCH_2NH.C(:NH)NH_2 + H_2O \rightarrow RCH_2NH_2 + CO(NH_2)_2$
   arginine ornithine urea

Apparently, other tissues do not have the property of converting ammonia into urea. Bollman and Mann[302] have demonstrated that after removal of the liver there is cessation of urea formation, and that urea is not formed when ammonia is injected; the ammonia escapes into the urine and tissues where it is

found as ammonium salts. Krebs and Henseleit,[322] using tissue slices, also observed that the liver is the only organ in the body capable of converting ammonia into urea.

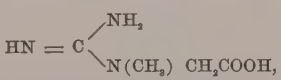
Ammonia.—Although the content of ammonia in the blood is very low (0.1 mg. per 100 ml.) the amount found in the urine may be as high as 1.0 gram per day. The reason for this difference is that ammonia is formed in the kidney. The best evidence for this formation has been obtained by Nash and Benedict[333] who observed that the ammonia content of the renal vein is higher than that of the systemic arterial or venous blood. It was shown also that the injection of acid or alkali, which is known to change the amount of ammonia in the urine, has no effect on the ammonia content of the systemic circulation. Nash and Benedict postulated that urea is the source of urinary ammonia. Another source may be the deaminization of amino acids in the kidney, for Krebs[321] has shown that kidney slices have the power to split off the amino group from amino acids and so produce ammonia. On the other hand, in dogs from which the liver had been removed, Bollman and Mann[302] were unable to show that amino acids have any effect on ammonia formation, whereas the administration of urea was accompanied by a marked rise in the urinary ammonia.

Urinary ammonia plays an important role in the regulation of the acid-base balance of the body. Following injection of acids or the production of fixed acids in the body, ammonia formation by the kidney is increased. Assuming that the ammonia comes from urea, the following reaction may take place:

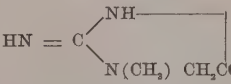
$$(NH_2)_2CO + 2NaCl + H_2CO_3 + 2H_2O \rightarrow 2NH_4Cl + 2NaHCO_3.$$

The ammonium chloride is eliminated by the kidneys, leaving the sodium bicarbonate available for neutrality regulation. Alkalosis produced by bicarbonate administration or hyperventilation reduces the output of ammonia in the urine.

Creatine and Creatinine.—These substances are products of nitrogenous metabolism, although some of the creatine and creatinine present in the food may appear in the urine. Creatine (methyl guanidine acetic acid),



is found chiefly in the muscles, although small traces may be demonstrated in the brain, testes, and other organs. Creatinine, an anhydride of creatine,



is related to creatine both chemically and physiologically. By means of his colorimetric method for the determination of creatinine, Folin[310] found that in any one individual the output of this substance is constant. The quantity of creatinine excreted does vary with different persons. The chief factor is the weight of the individual. Therefore, it is convenient to express the output of this substance in terms of the *creatinine coefficient.* This coefficient is obtained by dividing the amount of creatinine in milligrams excreted in twenty-four hours by the body weight in kilograms. In men the coefficient varies be-

tween 20 and 26; in women lower values ranging from 14 to 22 are found. The difference depends on the relative degree of muscular development in the two sexes.

Following the ingestion of creatinine, the greater portion of it may be recovered from the urine, whereas creatine must be taken in large quantities before any appears in the urine. When creatine does come through in the urine under these conditions, it is accompanied by a small amount of creatinine (Benedict and Osterberg[296]). From these experiments it appears that the body is able to store or oxidize creatine and to convert part of it to creatinine. Creatine is not found in the urine of adults on a normal diet, but it is a normal constituent of the urine of children and it appears during starvation.

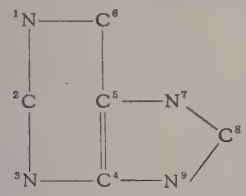
Many theories have been proposed to explain the origin of creatine in the body. Beard and Barnes[294] fed proteins and various amino acids to rats, and found that these substances increased the creatine content of the muscles and augmented the creatinine output. They concluded that creatine formation and creatinine excretion are directly due to the feeding of these large quantities of proteins and amino acids or that these substances indirectly stimulate the mechanism of formation of these substances. In a discussion of this work Rose[336] comes to the conclusion that the latter explanation is the correct one and that the apparent stimulation is of a nonspecific character. In patients suffering from progressive pseudohypertrophic muscular dystrophy, ingested creatine is recovered quantitatively in the urine. Brand and his associates[306] reported that feeding glycine to these patients increases creatine excretion 40 per cent above the control level. Abderhalden and Buadze[288] claim that nucleic acids and histidine are effective in raising the output of creatinine. It is impossible to determine by such experiments whether the extra creatine and creatinine are formed from the ingested substances or whether they are produced by some indirect process.

The use of tagged molecules has been extremely valuable in the study of creatine metabolism. Bloch and Schoenheimer[299] have shown that the administration of isotopic nitrogen in creatine was followed by the appearance of isotopic nitrogen in the creatinine of the urine. When isotopic nitrogen in creatinine was given to an animal, all of the isotopic material was recovered in the creatinine of the urine and none was found in the creatine of the body. These facts demonstrate that the reaction of creatine to creatinine is irreversible in the animal body. Heavy nitrogen in glycine or ammonium citrate fed to animals has been recovered in the glycine moiety of creatine (Schoenheimer et al.[300]), and N^{15} in the amidine group of arginine has been found transferred to the creatine molecule (Block and Schoenheimer[301]). By placing deuterium in the methyl group of methionine, du Vigneaud and his associates[353] have proved that this group is removed biologically to form the methyl group in creatine. Glycocyamine added to kidney and liver slices increased the production of creatine by these tissues (Borsook and Dubnoff[305]). These results make the origin of creatine clear; it is derived from the methyl group of methionine, the amidine group from arginine and the glycine part from glycine fed or produced in the body.

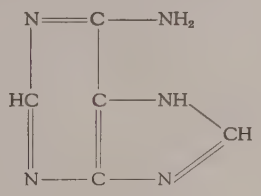
The importance of phosphocreatine in muscular contraction is discussed in Chapter LII.

Uric Acid.—The amount of uric acid found in the urine of man is very small; it varies from 2.5 to 5 mg. per 100 ml. In birds and reptiles this sub-

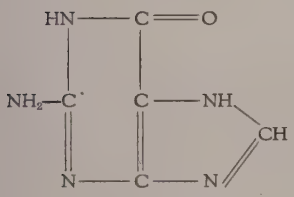
stance takes the place of urea as the chief end product of protein metabolism. For example, from 60 to 70 per cent of the nitrogen excreted in the urine of the goose is in the form of uric acid. This fact led to the idea that in man uric acid may be formed from proteins. Modern work has shown, however, that most, if not all, of the uric acid in the urine of man comes from the metabolism of purines and not from the breakdown of protein. The source of purines in the body is the nucleoproteins, which are complex substances composed of proteins and nucleins. The nucleins, in turn, may be hydrolyzed into nucleic acids and protein. Nucleic acids are found in the nuclei of cells; they probably do not occur in the cytoplasm. A nucleic acid is chemically complex, being composed of phosphoric acid, a pentose and purine base or pyrimidine. In the animal body three purine bases have been found: adenine, guanine, and hypoxanthine. These substances are readily oxidized to uric acid. The chemical similarity between these compounds and uric acid are shown by their structural formulas:



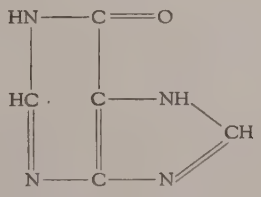
hypothetical purine skeleton



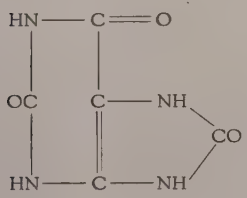
adenine
(6—aminopurine)



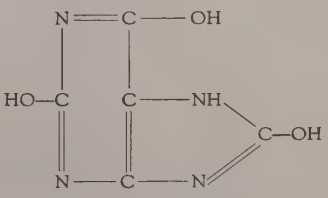
guanine
(2—animohypoxanthine)



hypoxanthine
(6—oxypurine)



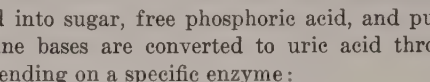
uric acid (lactim structure)



uric acid (lactam structure)

Two formulas are given for uric acid, the lactim and lactam; uric acid in solution may be made up of a mixture of these two forms.

Catabolism of Nucleic Acid.—Gastric and pancreatic juices split off the proteins attached to the nucleic acids and the intestinal secretions complete the splitting of the acid into sugar, free phosphoric acid, and purine bases. After absorption the purine bases are converted to uric acid through a number of steps, each step depending on a specific enzyme:



Bollman and Mann[303] have shown that the uric acid content of the blood increases after removal of the liver. Therefore, these reactions may take place elsewhere, probably chiefly in the muscles.

Excretion of Uric Acid.—A subject on a purine-free diet continues to excrete uric acid. This is derived from the purine constituents of the animal's own tissues and is referred to as *endogenous* uric acid. The endogenous purine metabolism is affected slightly by alteration of the protein intake. Folin, Berglund and Derick[312] have shown that high protein feeding increases the output of uric acid in the urine but decreases the blood uric acid. They concluded that the protein ingestion acts by accelerating the activity of the kidney in getting rid of the uric acid rather than by increasing its production. The source of the endogenous uric acid has been placed in the muscles, although Krafka[319] has presented evidence that it may come from destruction of the nuclei in the formation of red blood cells. In dogs he found a marked increase in the output of uric acid after hemorrhage, the output decreasing as the number of normal (nonnucleated) red blood cells increased. Confirmatory evidence was obtained by finding an increase in uric acid excretion when anemia was produced by phenylhydrazine hydrochloride.

The *exogenous* uric acid comes from the metabolism of the ingested purines. Thymus, pancreas, liver, and kidney contain considerable amounts of purine bases. Other sources are coffee, cocoa, and tea which contain methyl-purine derivatives. Some of the vegetables, peas, beans, and spinach, contain considerable amounts of these substances. Part of the ingested purine is excreted as uric acid; the amount depends on the particular purine base. Mendel and Lyman[332] showed that 64 per cent of ingested hypoxanthine, but only 37 per cent of adenine, is converted into uric acid. The remainder is apparently converted into unknown compounds. Compounds containing adenine have been shown to play an important role in the chemistry of muscular contraction (see Chapter LII).

THE CONTROL OF PROTEIN METABOLISM

Much less is known of the control of protein metabolism than of the control of carbohydrate or of fat metabolism. When insulin is injected into a diabetic, there is a fall in urinary nitrogen. This may be interpreted as a shift in metabolism from protein to carbohydrate under the influence of this hormone. However, Janney and Shapiro[316] have shown that insulin and glucose in a normal human subject have a greater sparing action of protein than glu-

cose alone. Mirsky[330] using, as an index of protein utilization, the nonprotein nitrogen concentration in the blood after nephrectomy, demonstrated a decrease in the nonprotein nitrogen and amino acid concentrations. MacKay, Barnes and Bergman[328] have shown a greater retention of nitrogen in rats injected with insulin. These results indicate that insulin either increases the utilization by the tissues of amino acids, for protein formation decreases the rate of deamination in the liver, or is operative by use of both processes.

The pituitary may play a role in protein metabolism. Extract of the anterior pituitary gland causes a fall in the nonprotein nitrogen of the blood (Teel and Watkins[343]) and a retention of nitrogen (Gaebler and Price[314]). Mirsky[331] showed that anterior pituitary extract increases the breakdown of protein in the muscle of a depancreatized animal. He assumes that in the intact animal the pituitary extract calls forth extra insulin, which counteracts the direct effect of the anterior pituitary extract on the muscle protein and which may decrease the utilization of amino acids in the liver. Additional evidence that the pituitary gland may control protein metabolism is furnished by a study of the blood sugar level in an hypophysectomized dog. In starvation, the blood sugar falls more rapidly than in a normal animal, but on a protein diet it is maintained (Soskin et al.[341]). This indicates that an animal without its pituitary gland is unable to mobilize its own amino acids for conversion into sugar but can use exogenous protein for that purpose. Adrenal cortical hormone also has an effect on protein metabolism, since gluconeogenesis is accelerated (see Chapter LI).

CHAPTER LV

THE METABOLISM OF FATS

GENERAL METABOLISM OF FATS

The fats have many important functions in the animal body. Their chief use is to serve as a store of potential energy. In this capacity they may be deposited by the body in almost unlimited amounts for utilization during future periods when the intake of food material is diminished or the expenditure of energy is increased. In addition, fats enter into the composition of many of the important structures of the body such as the nerve sheaths. They act as carriers for several of the vitamins and some of the fats are themselves essential for life. The sterols, substances related to fats, enter into the chemical constitution of hormones, vitamins and bile salts.

Classification of Fats.—Under the general heading of *lipids* the fatty acids and the compounds of fatty acids used in animal metabolism have been grouped by Bloor[361] as follows:

A. Substances having the following characteristics:
   1. Insolubility in water and solubility in fat solvents (e.g., ether, chloroform and benzene).
   2. Relationship to the fatty acids as esters, either actual or potential.
   3. Utilization by living organisms.

B. The following substances possess these qualifications:
   1. *Simple lipids:* Esters of the fatty acids with various alcohols.
      a. *Fats;* esters composed of fatty acids and glycerol.
      b. *Waxes;* esters composed of fatty acids and alcohols other than glycerol.
   2. *Compound lipids:* Esters of the fatty acids containing groups in addition to an alcohol and fatty acids.
      a. *Phospholipids:* Substituted fats containing phosphoric acid and nitrogen. Examples, lecithin and cephalin.
      b. *Glycolipids:* Compounds of fatty acids containing a carbohydrate and nitrogen but no phosphoric acid. Example, the cerebrosides.
      c. Aminolipids, sulfolipids, etc.: Groups which are not characterized sufficiently for classification.
   3. *Sterols:* Large molecular alcohols, found in nature combined with fatty acids. Example: cholesterol.

Absorption of Fats.—Following ingestion fat is broken down into glycerol and fatty acid by the action of the enzymes present in the gastric, pancreatic and intestinal juices. The major portion of this splitting occurs in the intestine where digestion and absorption of fat are aided by the bile. In the duodenum, the free fatty acids are neutralized by the alkaline secretions to form soaps. During the passage of the fatty acids and glycerol through the intestinal wall these substances are reunited to form neutral fat (see Chapter LXVIII). This

process may involve an intermediate phosphorus compound, for, as Sinclair[404] has demonstrated, there is a change in the phospholipid fatty acids of the intestinal mucosa while fat is being absorbed. Whether or not this is an obligatory intermediate between the fatty acid and neutral fat is not known. The fats are transported chiefly through the thoracic duct to the blood stream although other channels are present (Lee[390]).

Blood Fat.—The various lipids in the blood have been studied by several investigators. A summary of these results is given in Table LXXVIII. The com-

TABLE LXXVIII

LIPIDS IN NORMAL HUMAN PLASMA (FROM PAGE, KIRK, LEWIS, THOMPSON, AND VAN SLYKE[394]) THE RESULTS ARE IN MG. PER 100 ML. OF PLASMA

AUTHORS	NUMBER OF SUBJECTS	CHOLESTEROL TOTAL	CHOLESTEROL FREE	PHOSPHATIDES	NEUTRAL FATS	TOTAL LIPIDS
Man and Peters, 1933	12	207	—	229	—	659
Boyd, 1935	8	177	52	185	131	582
Van Slyke, *et al.*, 1935	66	232	82	181	225	735

position and the amount of blood fat are affected by the ingestion of this foodstuff. Leathes and Raper[388] have summarized the changes in blood fat occurring after a meal as follows: (a) the amounts of fatty acids in different combinations increase in plasma and corpuscles; (b) the amount of cholesterol tends to increase up to a certain maximum; (c) the amount of phospholipid increases, and it appears that the newly formed phospholipid is made from the absorbed fatty acids; (d) the cholesterol esters increase, chiefly in the corpuscles.

Storage of Fat.—The distribution of reserve fat has been studied quantitatively by Mendel and his associates;[397] their results are given in Table LXXIX. The amount of fat in these depots depends mainly on the quantity

TABLE LXXIX

DISTRIBUTION OF RESERVE FAT IN A RAT (FROM REED, YAMAGUCHI, ANDERSON AND MENDEL[397])

	PROPORTION TO TOTAL FAT (PER CENT)
Subcutaneous	50
Genital	20
Perirenal	12
Mesenteric	10
Intermuscular	5
Omental	3

of fat in the diet and the demand for energy. Reed, Anderson and Mendel[396] found that in rats more fat is stored on a diet rich in this substance than on one rich in carbohydrate, while exercise decreases the total amount but increases the relative amount of intermuscular fat. The type of fat in the storage depots varies with the type fed the animal. Lebedeff[30] starved two dogs until their normal supply of fat was depleted. To one of these dogs he fed mutton tallow and to the other linseed oil and later found that the fat laid down by these animals resembled the fat ingested by each. Other methods have been devised to study fat storage. For example, phenyl or a halogen groups may be intro-

duced into the fatty acids ingested and later these may be detected in the storage depots. The most recent experiments of this type have been made by Schoenheimer and his associates[401] who substituted deuterium (heavy isotope of hydrogen) for some of the hydrogen of the fat molecule. Their results showed that most of the ingested fat containing deuterium found its way to the fat depots while only a small fraction was present in the cells of the internal organs. They concluded that the ingested fat is deposited before use. It may be, however, that the animal is not able to oxidize fats containing foreign substances as readily as the normal fats and, therefore, these fats are shunted into the fat storage depots.

All of the fat does not disappear from the tissues during starvation. This fact has led to the concept that a certain amount of the fat in a tissue is an essential part of that tissue while the remainder is present as storage material. The essential portion is constant in amount while the storage fat varies with the amount present in the diet and with the metabolic activity of the issue.

The liver may act as a temporary storage place for fat as well as for carbohydrate. During this period of storage, the liver converts the fatty acids into lecithin which may be easily transported to the fat depots. Sinclair[404] has described two types of phospholipids in the liver: the one containing highly unsaturated fatty acids, the other containing ordinary food fats. He has proposed the interesting theory that the first is the structural phospholipid, and the second is the metabolic phospholipid which has to do with transport and metabolism of the fat obtained from food. Chaikoff and his associates[375] have studied the distribution of radioactive phosphorus (page 723) after ingestion of labeled phosphate. Immediately after ingestion, the intestinal tract, liver, and kidney show the highest content of phospholipid containing the radioactive phosphorus; however, the brain does not reach its maximal content until 200 hours later. These results indicate that the liver and intestine have the ability to form phospholipids quickly. *In vitro* studies with radioactive phosphorus have given a similar result.[398]

Under certain conditions, large amounts of fat accumulate in the liver. This fat is neutral fat, for the content of phospholipid during its accumulation remains constant. Bloor[362] has summarized the circumstances under which fat accumulates as follows: (1) in depancreatized dogs on certain mixed diets with insulin treatment; (2) after high-fat, low-protein diets; (3) after cystine feeding, but not after methionine feeding; (4) after cholesterol feeding; (5) during fasting if there is available fat in the depots; (6) after anterior pituitary extract injections; and (7) in the hen at onset of sexual maturity. The control of some of these processes will be discussed in the next chapter.

Cholesterol.—The sterols have many important functions in the body, for they enter into the composition of hormones, vitamins, and the cellular structure of some organs. They aid also in the saponification of fats by the action of bile. Some of the sterols, such as cholesterol, can be formed by the body from fats, because, as Eckstein[381] has shown, more cholesterol is formed on a high fat diet than on a low. Schoenheimer and Breusch[400] found that mice on a diet of bread synthesize as much cholesterol in a month as was initially contained in their bodies. The amount formed depends on the need, for when large amounts of cholesterol are given, there is a breakdown of this substance in the animal body.

SPECIAL METABOLISM OF FATS

There are four different pathways for oxidation of fat: β-oxidation, ω-oxidation; combined β- and ω-oxidation, and desaturation.

β-Oxidation.—By feeding various phenylated compounds of fatty acids, Knoop[386] succeeded in obtaining derivatives of the lower fatty acids. Depending on the length of the chain of the fatty acid either hippuric or phenaceturic acid appeared in the urine. These compounds are formed by the reaction of glycine with benzoic or phenylacetic acid:

1. $C_6H_5COOH + CH_2NH_2COOH \rightarrow C_6H_5CONHCH_2COOH + H_2O$
(benzoic acid) (glycine) (hippuric acid)

2. $C_6H_5CH_2COOH + CH_2NH_2COOH \rightarrow C_6H_5CH_2CONHCH_2COOH + H_2O$
(phenylacetic acid) (glycine) (phenaceturic acid)

The results obtained by Knoop when various phenyl derivatives of fatty acids were fed are given in Table LXXX. In these experiments fatty acids with an

Table LXXX

Oxidation Products of Phenyl Fatty Acids (From Knoop[386])

ACID FED		OXIDATION PRODUCT	EXCRETED AS
Benzoic acid	C_6H_5COOH	not oxidized	Hippuric acid
Phenylacetic acid	$C_6H_5CH_2COOH$	not oxidized	Phenaceturic acid
Phenylpropionic acid	$C_6H_5CH_2CH_2COOH$	C_6H_5COOH	Hippuric acid
Phenylbutyric acid	$C_6H_5CH_2CH_2CH_2COOH$	$C_6H_5CH_2COOH$	Phenaceturic acid
Phenylvaleric acid	$C_6H_5CH_2CH_2CH_2CH_2COOH$	C_6H_5COOH	Hippuric acid

odd number of carbon atoms gave rise to hippuric acid while those with an even number formed phenaceturic acid. Knoop explained these results by assuming that oxidation takes place in steps, each step consisting in throwing off the two carbon atoms adjacent to the — COOH group (β-oxidation):

$C_6H_5CH_2CH_2CH_2CH_2COOH \rightarrow C_6H_5CH_2CH_2COOH \rightarrow C_6H_5COOH$
(phenylvaleric acid) (phenylpropionic acid) (benzoic acid)

Additional evidence that this type of oxidation takes place was given by Embden[382] who found in liver perfusion experiments that fatty acids with an even number of carbon atoms give rise to acetoacetic acid while those with an odd number disappear. His results are given in Table LXXXI.

Table LXXXI

Acetoacetic Acid Formation From Fatty Acids (From Embden[382])

NORMAL FATTY ACID	NO. OF C ATOMS	FORMATION OF ACETOACETIC ACID
Acetic acid	2	variable
Propionic acid	3	–
Butyric acid	4	+
Valeric acid	5	–
Caproic acid	6	+
Heptylic acid	7	–
Octoic acid	8	+
Nonoic acid	9	–
Decoic acid	10	+

These results were explained by assuming, as Knoop had done, that oxidation takes place at the β-carbon atom and so gives rise to acetoacetic acid when the compound contains an even number of carbon atoms:

1. $CH_3CH_2CH_2COOH \rightarrow CH_3COCH_2COOH$
   (butyric acid) (acetoacetic acid)
2. $CH_3CH_2CH_2CH_2COOH \rightarrow CH_3CH_2COCH_2COOH$
   (valeric acid) (3-ketovaleric acid)

In the case of a fatty acid with an odd number of carbon atoms in the chain acetoacetic acid is not formed (Equation 2).

A third type of experimentation which shows that β-oxidation takes place has been employed by Quastel and his associates.[385] They measured the amount of acetoacetic acid formed by slices of liver (guinea pig) following the addition of various fatty acids. Their results are given in Table LXXXII. With this sensitive method, results similar to those of Embden were obtained, although the fatty acids with an odd number of carbon atoms did give slight amounts of acetoacetic acid.

TABLE LXXXII

FORMATION OF ACETOACETIC ACID FROM FATTY ACIDS (FROM QUASTEL AND JOWETT[385])

FATTY ACID	NO. OF C ATOMS	QAC. (MG. ACETOACETIC ACID PER MG. OF TISSUE PER HOUR)
Acetate	2	0.38
Butyrate	4	3.06
Valerate	5	0.95
Hexonate	6	2.93
Heptanoate	7	0.80
Octanoate	8	2.22
Decanoate	10	0.81
Control	—	0.25

A fourth type of experimentation which has demonstrated a difference in the catabolism of the odd and the even carbon fatty acids is the study of the ability of various fatty acids to form glycogen in the liver. Deuel and his associates[379] have shown that the odd chain fatty acids, propionic, valeric, heptoic, and nonylic, aid in the formation of glycogen, but the even chain ones do not.

ω-Oxidation and Combined ω- and β-Oxidation.—Another type of oxidation is the ω-oxidation. Verkade and van der Lee[407] found that dicarboxylic acids are formed from certain fatty acids fed to human subjects. They explained their results by assuming that oxidation takes place at both ends of the chain, a combination of ω- and β-oxidation:

$$CH_3CH_2CH_2(CH_2)_nCH_2CH_2COOH \xrightarrow{\omega\text{-oxidation}} HOOCCH_2CH_2(CH_2)_nCH_2CH_2COOH$$
two sided β-oxidation
$$\rightarrow HOOC(CH_2)_nCOOH$$

The relative importance of ω-oxidation as contrasted with β-oxidation is not known. ω-oxidation does not give rise to ketone bodies but does give succinate. Therefore, this type of oxidation does not explain the production of ketone bodies during abnormal types of metabolism, but does explain fat transfer to carbohydrate, since succinate can be converted readily into glucose by animal tissues.

Desaturation.—The fourth type of oxidation of the fatty acid molecule is desaturation, or removal of hydrogen. Leathes and Raper[388] have summarized the evidence in support of the view that fats are transported from the storage deposits to the liver where the first step in their metabolism is a desaturation. The evidence for this metabolic change has been obtained by feeding rats cod liver oil (Leathes and Meyer-Wedell[387]), since on this diet, the fat in the liver has a higher iodine value than the ingested fat. Additional recent evidence has been supplied by Schoenheimer and his associates[402] using deuterium labeled fat. Their experiments show that saturation and desaturation of fatty acids occur constantly. It has been suggested that the process of desaturation is not primarily for complete oxidation but merely to make a fat liquid at the temperature of the body. Whatever the purpose may be, it is a form of oxidation.

Ketone Body Formation.—In the previous sections, the end products of the metabolism of the fatty acids with an even number of carbon atoms were given as follows: acetoacetic acid, acetone and β-hydroxybutyric acid. These substances, called ketone bodies, do not appear in the blood or urine under normal circumstances. However, under abnormal circumstances such as carbohydrate starvation or diabetes mellitus, large quantities of ketone bodies accumulate in the blood and urine. Under such abnormal conditions the carbohydrate supply is reduced and the products of incomplete combustion of fat appear. If carbohydrate is given to a starving subject, or if insulin is injected into a diabetic, the ketone bodies disappear. These facts illustrate that there is a direct or indirect connection between fat and carbohydrate metabolism.

Various questions arise as to the quantitative production of ketone bodies from fat, and the quantity of carbohydrate in the food, necessary to prevent ketone body formation. The older idea was that one molecule of fat gave rise to one molecule of a ketone by successive β-oxidation of the fatty acid. This process, supposedly, stopped at the ketone stage. These products were looked upon as waste products which disturbed the acid-base equilibrium of the blood and depleted the body of base in their excretion. In order to return the body to its normal state, all of the ketone bodies had to be excreted by the kidneys. Modern work has revised these concepts. Jowett and Quastel,[385] from their study of the formation of ketone bodies in liver slices, have shown that the higher fatty acids can give rise to more than one molecule of ketone. Deuel[19] and his associates, from feeding experiments, came to a similar conclusion. Blixenkrone-Møller,[373] using the perfused liver, and Stadie and his associates,[406] using liver slices, have calculated, from their experimental data, the molecular ratio of oxygen used for ketone formation and they have concluded that this ratio demonstrates that fat may be broken into multiple ketones:

$$\underset{\text{palmitic acid}}{C_{16}H_{32}O_2} + 5\ O_2 = 4\ \underset{\beta\text{-hydroxybutyric acid}}{C_4H_8O_3}$$

These numerous facts demonstrate that a multiple formation of ketones takes place from the higher fatty acids and that the older idea of only one molecule of ketone coming from a fatty acid molecule must be given up.

A second assumption formerly made was that ketone bodies are not used by the body but are entirely excreted. Perfusion experiments by Blixenkrone-Møller[373] have demonstrated that resting muscles are able to use ketone bodies and that stimulation accelerates this utilization. More recently, Stadie and his associates[406] have shown that minced muscle may use acetoacetic acid.

The question as to the amount of carbohydrate necessary to prevent ketone body formation was studied by Shaffer.[399] Taking into consideration the amount of sugar that may be derived from protein and fat, he proposed the following formula for calculating the carbohydrate necessary to prevent ketone body formation:

$$\text{Ratio} = \frac{2.4P + 3.43F}{3.2P + 0.57F + 5.56G}$$

In this formula P, F, and G represent grams of protein, fat and glucose metabolized.

The foregoing facts showing that a fatty acid molecule gives rise to more than one ketone body and that ketone bodies may be used by muscle, affect the theoretical implications in this calculation. Therefore, the ratio can only be used as a rough approximation of the relative amounts of food material ingested to prevent ketone body formation. Generally a ratio of 2:1 is taken for the minimal amount of carbohydrate needed for the prevention of ketone body formation.

The fact that the presence of adequate sugar in the liver diminishes the ketone body production may be explained in two ways: either the oxidation of carbohydrate aids in the oxidation of ketone bodies, a ketolytic process; or the metabolism of glucose inhibits the formation of these substances, an antiketogenic method. Mirsky and his associates[393] have presented considerable evidence to show that there is competition for substrates in the liver. When glucose is present, glucose is oxidized by preference; whereas if glucose is absent or low in concentration, then fat is used and ketone bodies are formed. Therefore, there is only an indirect connection between the oxidation of fats and carbohydrates. It might be said, however, that the process is one of antiketogenesis.

Ketone bodies are formed by the liver to meet the need of the muscles when carbohydrate supplies are low. Thus, they are useful metabolites and not waste products of fat metabolism.

THE CONTROL OF FAT METABOLISM

Although the control of fat metabolism is not as clearly defined as the regulation of carbohydrate metabolism, numerous factors, neural, endocrine and vitamin, have been described which affect fat metabolism.

Neural Control.—The only definite experimental evidence of neural control has come from a study of lesions in the region of the hypothalamus. Studies of the effects of such lesions have demonstrated that this part of the brain is concerned with fat metabolism. Smith,[405] by injection of chromic acid into

TABLE LXXXIII

EFFECT OF LESIONS IN THE HYPOTHALAMUS ON DISTRIBUTION OF FAT IN RATS (FOSTER AND BENNINGHOVEN[383])

	ANIMALS WITH HYPOTHALAMIC LESIONS	NORMAL CONTROL ANIMALS
Body weight, grams	539	238
Water in body, per cent	29	62
Fat in body, per cent	58	16
Liver fat, per cent	24	36

the hypothalamus, produced an increase of over 100 per cent in the body weight of rats. This increase in weight was due to the accumulation of fat. Some of the analyses made by Foster and Benninghoven[383] on these animals are given in Table LXXXIII. It may be seen in this table that 58 per cent of the body weight of the experimental animal was fat in contrast to 16 per cent in the control animal. A similar increase in weight in the monkey has been described by Ranson and Ingram[395] and by Brooks[374] following hypothalamic lesions. Exact metabolic studies on these animals have not been made, especially as to their intake of food. The accumulation of fat may be secondary

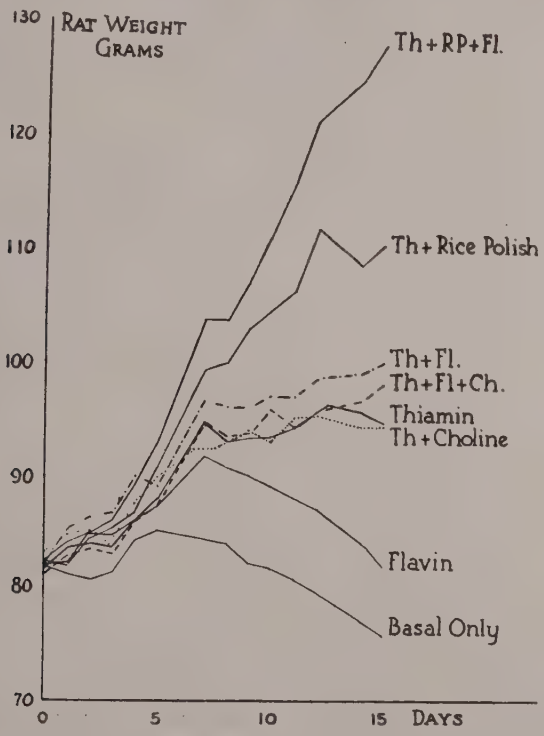


Fig. 297.—Effect of B vitamins on body weight. (From McHenry and Gavin: J. Biol. Chem. 125: 657, 1938.)

to some other change causing an increase of appetite or a decrease in metabolism. These experimental findings show clearly, however, that the hypothalamic region controls the deposition of fat.

There is no good evidence at the present time that peripheral nerves or the sympathetic system may mobilize fat.

Hormonal Control.—Numerous extracts from the endocrine glands affect fat metabolism either directly or indirectly. Insulin, by allowing carbohydrate to be stored in the liver, indirectly decreases fat metabolism and the produc-

tion of ketone bodies. Extracts from the anterior pituitary gland cause an increase of the ketone bodies in blood and urine, and an accumulation of fat in the liver (MacKay and Barnes;[391] Best and Campbell[372]). By using fat tagged with deuterium, Best and his associates[367] have shown that the fat which accumulates in the liver comes from fat depots. Therefore, this extract has the ability to mobilize fat from the storage regions.

The fact that fat accumulates in the liver of a depancreatized dog which has been fed insulin, suggests that there may be a fat-controlling hormone in the pancreas which has a direct action on fat metabolism. Dragstedt[380] has described such a hormone, prepared from the pancreas, that has the property of preventing these fatty livers. He has called this hormone "lipocaic," meaning the "fat-burning" hormone. Dragstedt has shown that, in its preparation lipocaic is freed of choline and lecithin and, therefore, has a separate action from these two compounds.

Vitamin and Dietary Control.—In addition to the lipocaic control of the fatty livers in experimental diabetes, choline has also been shown to possess the property of removing this fat. This discovery resulted from a series of observations: first, that the feeding of raw pancreas to the diabetic (Hershey and Soskin[384]) is effective; then that lecithin acts efficiently; and finally, that choline (Best and Huntsman[369, 370]) is the active component in this compound. A working hypothesis of the action of choline has been given by Best[360]). Choline is essential in the formation of phospholipid in the liver. In its absence, neutral fat accumulates and the presence of an excess of fat in the liver decreases the liver function. These findings are of interest in connection with fat transport, since they illustrate the importance of the production of phospholipid for the mobilization of fat from the liver to the tissues.

Diets low in protein also produce fatty livers which may be restored to normal by dosage with casein (Best and Huntsman;[371] Channon[376]). The activity of casein is much less that of choline, for 1 gram of casein is required to equal the activity caused by 5 to 8 mg. of choline. The action of casein in this respect may be due to the presence of one or more active amino acids. Methionine has been shown to decrease the fat in fatty livers and tyrosine has a slight action. Cystine, on the other hand, produces fatty livers. Therefore, the final result of any ingested protein would depend on the relative amounts of the amino acids having the power to deposit or to remove fat from the liver. The actual chemical mechanisms involved are not known.

The Effect of Other Vitamins on Fat Metabolism.—McHenry and Gavin[392] have shown that a diet without choline but containing vitamin B_1 will cause large amounts of fat to accumulate in the liver. This increase in fat was greater than could be accounted for by the fat in the diet. It was demonstrated also that vitamin B_1 with riboflavin and rice polishing gives a greater effect than any one of these constituents. These results are illustrated in Fig. 297.

Various unsaturated fatty acids are essential for some of the functions of the body. These substances will be discussed in the chapter on Vitamins (Chapter LVI).

CHAPTER LVI

VITAMINS

A diet may be quantitatively adequate with regard to calories, essential amino acids, and inorganic elements, but may be incomplete for maintenance and growth unless it contains accessory food factors, the vitamins. These substances may be defined as essential constituents of the diet, organic in nature, incapable of synthesis by the body and effective in playing a part in the maintenance of the normal functioning of tissues in amounts minute by comparison with those of the foodstuffs which supply structural material and energy (Drummond[409]).

The reason that a discussion of vitamins is included in a textbook of physiology is that these substances play a prominent role in the control of metabolism similar to the hormonal control. In fact, they can be looked upon as hormones derived from plant sources. Their function, however, is not as spectacular as that of animal hormones whose activity can be measured in terms of minutes or hours. The absence of a vitamin may be revealed only after days or weeks of feeding a deficient diet; however, after that time, characteristic pathological symptoms show themselves. The delay in the appearance of symptoms is due in part to the fact that the animal body is able to store a small amount of the needed vitamins.

The lack of certain vitamins produces characteristic diseases of which beriberi, scurvy, and pellagra are outstanding examples. Scurvy, according to Garrison,[440] afflicted 75 per cent of the men of Lord Anson's fleet in 1740. Through the introduction of lime juice in 1795 scurvy disappeared from the British Navy, and, by 1797, not a single case was discovered. This was the first triumph for vitamins. Beriberi has claimed hundreds of victims and is still prevalent in eastern countries where the diet is chiefly rice. Sebrell[471] calculates that there are 100,000 cases of pellagra in this country. It is obvious that a knowledge of vitamins is essential, not only from a physiological view, but also from a medical and a public health standpoint.

One of the difficulties of studying vitamins is that different species do not require the same vitamins, and even when they do, different amounts are needed by the various ones. For example, only man, other primates, and guinea pigs do not have the ability to make ascorbic acid (vitamin C). Another difficulty has been that the terminology employed has been changed frequently with the advances in this field. Fortunately, because some of the vitamins are recognized as chemical compounds, the older terms are now being changed to their chemical names, thus giving definite meaning to the terminology.

Vitamins bridge the gap from the plant to the animal kingdom, for they are produced only in plants and are needed by animal tissues for carrying out fundamental metabolic processes. The first clear evidence that growth of animals is dependent not only on proteins, fats, carbohydrates, and salts but also on accessory factors was obtained from the experiments of Hopkins[453] (Fig. 298). Since then tremendous advances have been made in the field. The most outstanding achievement in recent years has been the discovery that certain

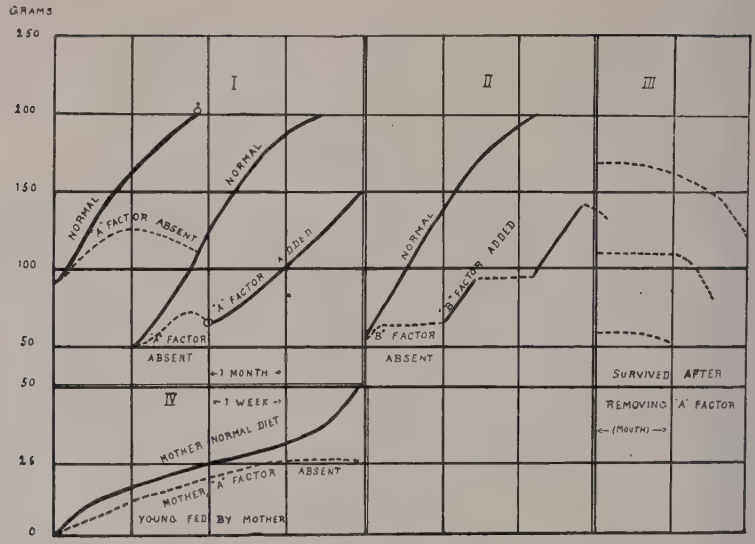


Fig. 298.—Curves of growth of rats as influenced by the accessory food factors. I. The effect of the "A" (fat-soluble) factor. Note that the curve does not immediately descend after removal of this factor from the diet. II. The effect of the "B" (water-soluble) factor. Note that growth ceases immediately after it is withdrawn. III. The time during which animals survive after removal of the "A" factor at different ages, the uppermost curve being that obtained for rats that were nearly mature before the factor was removed from the diet and the lower ones for less mature animals. IV. The continuous curve is for young fed by mothers receiving "A" factor in their diets; the broken-line curve is for young fed by mothers receiving none of this factor. (From Hopkins and Chick.)

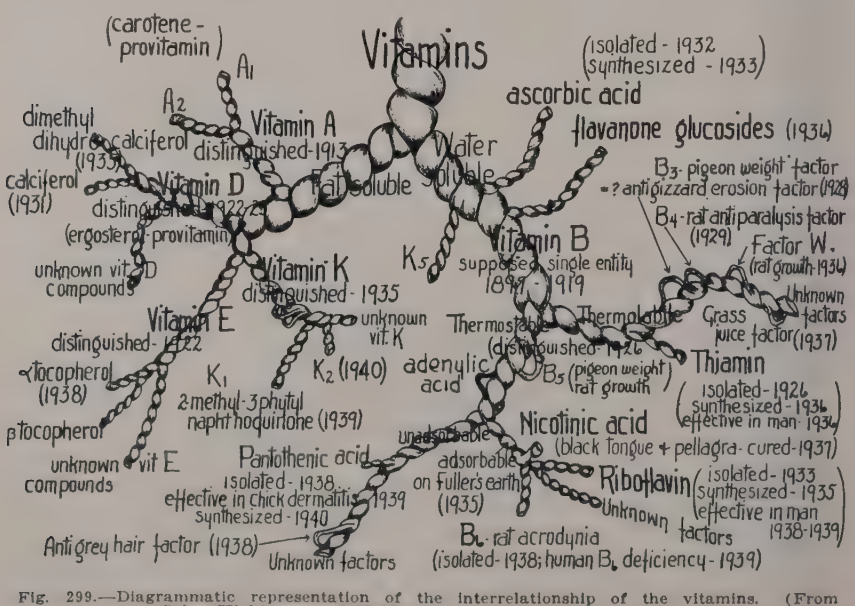


Fig. 299.—Diagrammatic representation of the interrelationship of the vitamins. (From Spies, Hightower and Hubbard: J. A. M. A. 115: 292, 1940.)

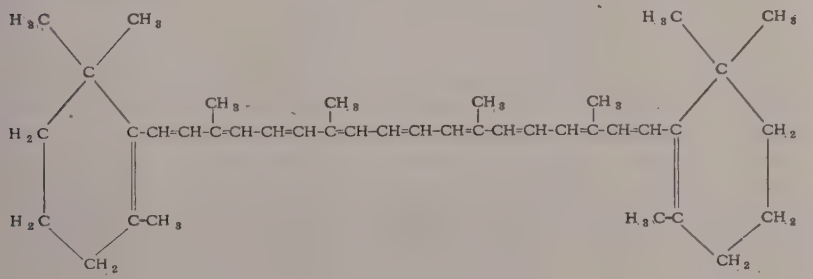
vitamins are concerned with coenzyme activity. This discovery has come through two independent developments, the study of cellular respiratory mechanisms as an enzymatic process and the study of vitamin deficiencies. Although all the manifestations of vitamin deficiency cannot be explained on the basis of cellular respiratory mechanisms, a start has been made and future advances may be anticipated along these lines.

Many vitamins have been described. On the basis of their biological activity, they are divided into several groups which were designated originally by the letters of the alphabet. They will be discussed in the order of the letters. Fig. 299 gives a diagrammatic representation of the interrelationship of the vitamins (Spies, Hightower and Hubbard[477]).

VITAMIN A

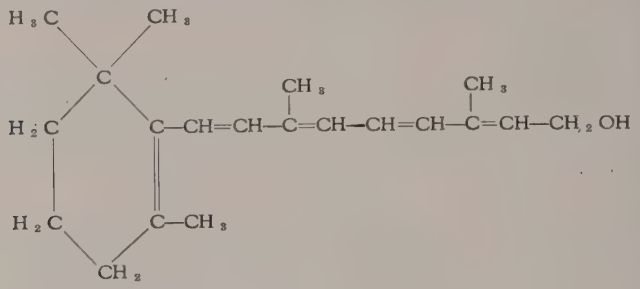
In the same volume of the *Journal of Biological Chemistry* (1913), McCollum and Davis[458] and Osborne and Mendel[465] independently reported the necessity of adding butter to a synthetic diet in order to obtain adequate growth in rats. Later, Osborne and Mendel noticed that animals receiving insufficient amounts of butter developed eye lesions. This pathological change in the eyes, known as xerophthalmia, is characterized by a drying of the cornea and conjunctiva with ulceration and degeneration. Cod liver oil has the property of preventing these lesions (Osborne and Mendel). This oil also prevents rickets, and it was once thought that a single vitamin controlled both conditions. McCollum and his associates[459] were able to show, however, that there are two distinct vitamins. Oxidation of cod liver oil destroys the power of this substance to cure xerophthalmia but does not remove the factor which prevents rickets (vitamin D). Therefore, vitamins A and D are separate substances.

Chemistry of Vitamin A.—Steenbock and his associates[472, 473] demonstrated a relationship between the presence of a yellow pigment (carotene) in plants and vitamin A. They observed that foods, such as carrots, yellow sweet potatoes, and yellow corn, are rich sources of vitamin A, while white corn is deficient. Although the yellow pigment is associated with vitamin A activity, there are colorless or almost colorless materials, such as cod liver oil, that have similar potency. Therefore, carotene is not vitamin A. The exact relationship between carotene and vitamin A was demonstrated by von Euler and his associates.[435] They showed that the administration of as little as 0.005 mg. of purified carotene per rat per day enabled the animals to grow normally. The obvious conclusion is that carotene is a precursor of vitamin A and that it may be readily changed into this vitamin in the animal body. There are several known isomers of carotene, α, β, and γ compounds, all of which may be converted into vitamin A. The formula for β-carotene is:



Cryptoxanthin, a compound closely related to carotene, also has precursor activity.

Vitamin A has been isolated in crystalline form by Holmes and Corbet.[452] It is an unsaturated alcohol and has the following formula:



The crystalline material has a biological potency of about 3,000,000 international units per gram. A chemical difference has been discovered between the vitamin A in the livers of salt and fresh water fishes (Gillam et al.[442]). The vitamin A described above is called A_1 and comes from salt water fish. A_2, from livers of fresh water fish, has an additional double bond. There may be other closely related compounds which have vitamin A activity.

The precursors of vitamin A are absorbed in the intestine from the ingested food material. They are carried to the liver where they are broken down into this vitamin. However, not all of the precursors are broken down immediately and thus the liver may act as a storehouse for vitamin A. There seem to be considerable differences between species as to their ability to utilize the precursors of vitamin A. Even in a single species there is considerable variation in utilization of the precursors when they are supplied in different foodstuffs.

A unit of vitamin A has been defined as the biological activity of 0.6γ of pure β-carotene. It is estimated that from 3,000-6,000 units are required for an adult per day. In plant foods, vitamin A is present only as a precursor, but in milk and butter both precursor and vitamin A are present. In fish oils, the active material is all in the form of vitamin A. Natural sources of vitamin A are yellow corn, spinach, carrots, prunes, butter, cheese, eggs, liver, and fish liver oils (Levine[413]).

Vitamin A Function.—The characteristic features of vitamin A deficiency in man have been summarized by Eusterman and Wilbur.[436] The absence of this vitamin in the diet produces, in addition to the failure of growth, two types of eye changes: night blindness (nyctalopia) and xerophthalmia. Night blindness is defined as the inability to adapt the faculty of vision to very faint illumination and is associated with changes in the visual purple (see Chapter XXIII). Fridericia and Holm[439] have shown that there is a delay in the regeneration of the visual purple in rats suffering from vitamin A deficiency. Wald[484] has demonstrated that the visual purple system uses vitamin A and is dependent on the presence of this vitamin in the diet for its replacement.

The relationship between dark adaptation and vitamin A has led to the use of an instrument, the biophotometer, for the study of this reaction. The test is based on the

changes occurring in the eyes of an individual when he is exposed to a brilliant light and later subjected to point illumination. Numerous types of this instrument have been devised (Hecht[448]). In applying the biophotometer test to a large number of individuals, there are definite limitations. For example, there is a learning factor which may render the test inadequate for mild degrees of vitamin A deficiency. Moreover, there is a marked variation in normal individuals which makes difficult the establishment of a normal threshold value of dark adaptation. In a study of four normal men on a diet low in vitamin A, Hecht and Mandelbaum[449] observed with a biophotometer that both cone and rod functions are disturbed by the lack of vitamin A and that they are restored by the addition of this vitamin to the diet.

Another eye lesion is xerophthalmia, which, in man, is characterized by drying of the cornea with corneal softening and secondary infection. In addition to the eye lesions, there are cutaneous changes consisting of a dry, scaly, shriveled condition of the skin. Changes in the bronchial epithelium have been described. In fact, vitamin A deficiency affects all the mucous membranes and the skin. The infections that develop are probably secondary. The "anti-infective" function of vitamin A claimed by some investigators has not been clearly established.

THE VITAMIN B COMPLEX

At one time, it was supposed that a single vitamin, B, had the property of preventing polyneuritis in pigeons and beriberi in man and of promoting growth in young animals. This vitamin, however, has been subdivided into numerous fairly distinct factors. Table LXXXIV gives a summary of these substances as they are at present designated.

TABLE LXXXIV

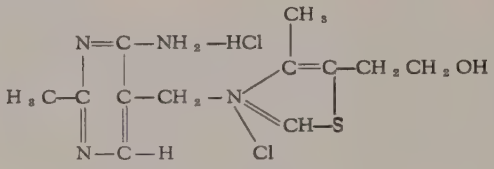
THE VITAMIN B COMPLEX

ALPHABETICAL NAME	CHEMICAL NAME	FUNCTION
B_1	Thiamin chloride	Antineuritic factor
B_2	Riboflavin	Preventative of skin lesions
B_3	----	Necessity for growth of pigeons
B_4	----	Preventative of paralysis in rats and chicks
B_5	----	Necessity for growth of pigeons
B_6	Pyridoxine	Antidermatitis factor for rats
P-P (Pellagra Preventive)	Nicotinic Acid	Preventative of skin lesions
Factor W	----	Growth factor for rats
----	Pantothenic Acid	Preventative of dermatitis in chicks

Vitamin B_1.—The first thorough experimental work on this accessory food factor was carried out by Eijkman[429] who noticed that fowls fed on polished rice develop a typical polyneuritis and exhibit symptoms similar to those characteristic of beriberi in human beings. Eijkman demonstrated that the addition to the diet of the material removed by the polishing cures these animals. Emmett and Luros[432] showed that there are two factors involved in the unmilled rice, the antineuritic vitamin (pigeons) which is destroyed by heating and the growth promoting factor (rats) which is heat-resistant. Goldberger and his associates[443] were able to demonstrate the dual nature of this vitamin by making an alcoholic extract of corn meal. Such an extract has the power of curing polyneuritis but does not contain the growth factor. Autoclaved yeasts which have the property of curing dermatitis, when added to the alcoholic extract, cure the polyneuritis and promote growth. These experiments divided vitamin B into two components; one which has the power of curing and pre-

venting polyneuritis and the other which prevents and cures dermatitis and allows growth to take place normally. Further subdivision has taken place. Vitamin B_1, at the present time, may be defined as a water-soluble, heat labile vitamin having the property of preventing avian polyneuritis and human beriberi.

The Chemical Nature of Vitamin B_1.—Williams and his associates[487] have obtained this vitamin in pure crystalline form and have given the following formula for its structure:



Vitamin B_1 (thiamin hydrochloride)

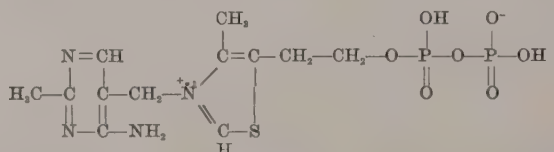
A clinical trial of the crystalline material has demonstrated its antineuritic activity.

Vitamin B_1 Function.—In human beings, deficiency of this essential food factor results in beriberi, a disease characterized by peripheral neuritis. There are two forms of this disorder: the wet and the dry. In the wet type, there is extensive edema of the extremities while the dry form is characterized by wasting and paralysis of the limbs. The gastrointestinal tract is also affected, for Cowgill and his associates[427] have shown in dogs that there is marked gastric atony in severe cases of deficiency of this vitamin.

Outstanding work in this field was the recognition that vitamin B_1 enters into an enzymatic reaction, converting a keto acid into an aldehyde, a decarboxylation:

$$CH_3COCOOH \rightarrow CH_3CHO + CO_2$$

As early as 1911, Neuberg and Hildesheimer[463] discovered that yeast contains an enzyme, carboxylase, which converts keto acids to aldehyde. In 1932 Anhaugen[421] demonstrated that carboxylase requires a coenzyme for its activity. This coenzyme was shown by Lohmann and Schuster[49] to be the pyrophosphoric acid ester of vitamin B_1.



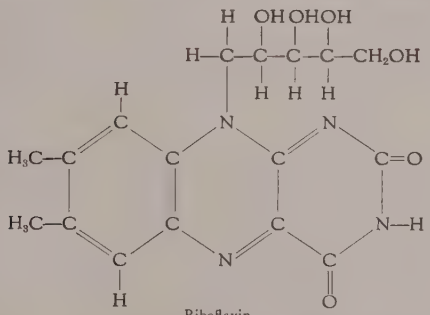
Cocarboxylase

Before this discovery, Peters and his associates[466] had studied the effect of vitamin B_1 on the metabolism of brain tissue of pigeons suffering from the lack of this vitamin. They had observed two effects: vitamin B_1 increases the oxygen uptake and decreases the formation of pyruvate by such brain tissue. Pyruvate accumulates in the blood of pigeons and rats suffering from vitamin B_1 deficiency (Thompson and Johnson[481]), and the amount present is increased by exercise in these vitamin B_1 deficient animals. These facts demonstrate that vitamin B_1 has the same activity in brain tissue as in yeast; namely, it aids in the oxidation of pyruvate, and in the absence of this vitamin pyruvate accumu-

lates. It has been demonstrated also that mammalian tissue has the ability of phosphorylating vitamin B_1 to form the coenzyme, cocarboxylase.

Cowgill[418] has recently reviewed the human requirements for vitamin B_1, and found that the amount needed varies with the size of the individual. He advises 280 international units for a man weighing 70 kg. and 550 units for a man weighing 90 kilograms. The international unit is defined as the vitamin B_1 activity of 3 micrograms of crystalline vitamin B_1. The natural sources of vitamin B_1 are wheat germ, bran, tomatoes, prunes, egg yolk, kidneys, oysters, yeast, and nuts (Levine[413]).

Riboflavin (Vitamin B_2).—It had long been recognized that the growth of rats requires a component formerly called B_2. Kuhn and his associates[445] noticed that the ability of a material to promote growth in rats is associated with a yellow color and green fluorescence which are characteristic of a class of compounds called flavins. Flavins have been isolated from milk, liver, heart, skeletal muscles, yeast and egg white. Following the synthetic production of flavins, it was demonstrated that their synthetic activity was similar to that of the naturally occurring product. The structural formula for riboflavin is:



Riboflavin

This substance does not cure black tongue in dogs or pellagra in man. There has been recognized for years a "pellagra sine pellagra" characterized by erosions at the angles of the mouth, and seborrhea about the nose which occurs in patients suffering with pellagra (see page 824). This led early workers to postulate that multiple dietary factors may be involved in this clinical condition. Sebrell and Butler[470] have recently shown that these lesions appear in human cases on diets low in riboflavin and are cured or prevented by giving the patient synthetic riboflavin but not nicotinic acid, which is the pellagra-preventive vitamin. The importance of riboflavin in cellular respiration is discussed in Chapter XLVIII. It is estimated that 2 to 3 mg. daily are necessary. The common sources of vitamin B_2 (Levine[413]) are spinach, carrots, lettuce, pears, bananas, dried prunes, milk, eggs, liver, beef, and brewer's yeast.

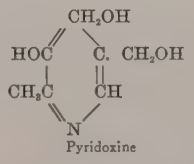
Vitamin B_3.—This factor may be defined as a substance required for full weight restoration in the pigeon on a diet which, in addition to vitamins B_1 and B_5, includes an adequate supply of basal dietary constituents, such as salts and proteins (Carter and O'Brien[425]). A pigeon receiving large doses of vitamin B_1 attains only about 80 per cent of its normal weight. If, however, an extract of liver is added to the diet, it grows normally. This extract has been subdivided into two effective factors by Carter and O'Brien.[425] The first factor is

adsorbed in fuller's earth and carries with it a flavin, while the other is present in the filtrate after treatment with fuller's earth. The adsorbed fraction has slight growth promoting activity, but the maximum effect is obtained only when both factors are combined in the diet. This vitamin is found in whole wheat, yeast, and liver.

Vitamin B_4.—Reader and her associates[467] have described two heat- and alkali-labile substances in water extracts of yeast. The one factor is B_1, already described, while the other is termed B_4. Reader gives the following symptoms as typical of vitamin B_4 deficiency. In addition to retarded growth, the rats show spastic gait, muscular weakness, and loss of coordination. A crystalline compound has been prepared that has vitamin B_4 activity. This compound has been identified as adenine which in itself has no power to protect rats from vitamin B_4 deficiency. The vitamin is probably carried with the adenine as an impurity. The natural sources of this substance are whole wheat, lettuce, milk, liver, and yeast.

Vitamin B_5.—Carter, Kinnesley and Peters[424] have described a factor, which is not identical with B_2, B_3, or B_4, but is necessary for the nutrition of the pigeon and have termed it vitamin B_5. They claim that three factors are necessary for nutrition in the pigeon, B_1, B_3, and B_5 while B_1, B_2, and B_4 are needed by the rat. Such conclusions illustrate the present complexity of the vitamin problem. It may be that different species require different nutritional factors of this type.

Pyridoxine (B_6).—In their studies on pellagra, Goldberger and Lillie[444] reported that a disease in rats characterized by dermatitis could be produced by the same deficient diets as those which produced black tongue in dogs and pellagra in man. Later work demonstrated that the lesions produced are not caused by a deficiency of nicotinic acid nor of riboflavin but are due to a separate substance (György[446]). This compound has been isolated (György[447]) and the following formula given:



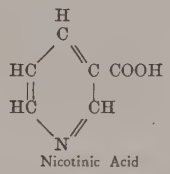
Pyridoxine

Rats are cured of dermatitis when fed 5 to 10 mg. of the hydrochloride of this material per day. Spies and his associates[476] have demonstrated that this compound has the property of curing a certain type of muscular weakness in man.

Factor W.—Elvehjem, Koehn and Oleson[432] have described another factor essential for the growth of rats kept on a deficient vitamin B diet to which adequate amounts of B_1, B_2, and B_4 were added. They concluded that this additional factor is necessary for the growth of rats.

Nicotinic Acid (Pellagra-Preventive).—Goldberger and his associates[443] showed that pellagra is a deficiency disease in man and that black tongue in dogs is analogous to pellagra in man. These two conditions are produced or cured by the same diets. The symptoms are similar, in that in both diseases there is stomatitis, diarrhea, secondary anemia, and dermatitis of the scrotum. The factor necessary for the cure of these conditions was called the pellagra-

preventive (P-P) factor by Goldberger, and was included in the old vitamin B_2 group. Elvehjem[431] showed that the compound which has the property of curing black tongue in dogs was nicotinic acid or its amide. Spies[475] and Fonts and his associates[438] applied this finding to patients and were able to cure human cases with the pure compound. The structural formula for nicotinic acid is:



Nicotinic Acid

The importance of nicotinic acid in cellular respiration was discussed in Chapter XLVIII in which it was pointed out that this substance enters into the pyridine nucleotides that form the coenzyme systems for oxidation of numerous substrates. The amount of this coenzyme is reduced in vitamin deficient animals.

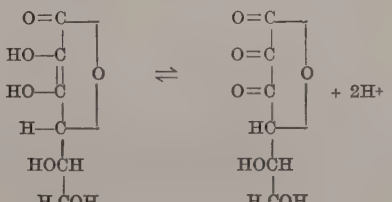
The requirement of nicotinic acid for normal man is from 10 to 25 mg. per day. Spies advises half a gram daily for curing pellagra.

Pantothenic Acid.—Williams[486] described a substance that accelerates the growth of yeast. Its activity is very great, for only 5 parts in 10 billion parts of culture medium are needed to produce an effect. In a later paper,[487] he and his associates showed that the calcium salt of this substance has the empirical formula $(C_8H_{14}O_5N)_2$ Ca. This substance turns out to be identical with a vitamin necessary for the cure of chick dermatitis (Woolley, Waisman and Elvehjem[488]).

VITAMIN C

Most of our knowledge concerning vitamin C has come from clinical observation because many animals do not require this factor. Guinea pigs are, however, very susceptible to its absence. When these rodents are fed on a diet of grain, their joints become swollen and tender, causing the animal to lie in such a position as to minimize the pain. The teeth become loose and can be pulled out readily. Postmortem examination reveals hemorrhages in the tissues of the limbs and alimentary canal. Similar symptoms and pathological changes are seen in scurvy in man.

Chemistry of Vitamin C.—It has been known for a long time that fruit juices have the property of preventing scurvy. Working independently, Waugh and King[485] and Svirbely and Szent-Györgyi[479] discovered that it is ascorbic acid which has antiscorbutic activity. Szent-Györgyi[480] had previously isolated this compound from the adrenal cortex and from plants. The following formulas have been given the l-form and its oxidized product:



l-Ascorbic acid Dehydroascorbic acid

Although ascorbic acid is a strong reducing agent and may be rapidly oxidized in vitro, it is relatively stable in the animal body. On account of its reducing property, many attempts have been made to find a definite place for ascorbic acid as a hydrogen carrier in tissue respiration, but as yet these have been unsuccessful.

Stotz and his associates[478] have demonstrated that ascorbic acid increases the oxygen consumption of guinea pig liver. Schultze, Stotz, and King[469] showed that the protein sulfhydryl groups have the power of reducing dehydroascorbic acid to ascorbic acid very readily. Gemmill and Hellerman[441] have shown that ascorbic acid has the ability to reactivate the muscle glycolytic systems, inactivated by oxidizing agents. It is surprising that such an active agent as ascorbic acid has not found a definite place in cellular respiration.

The l-form is the active substance, for the d-isomer has no activity. The international unit is, at the present time, 0.05 mg. of l-ascorbic acid. The daily requirement is considered to be from 30 to 60 mg. for the prevention of scurvy (Abt and Farmer). The natural sources for this vitamin are fresh corn, spinach, peas, lemons, oranges, strawberries, apples, milk, and liver (Levine[413]).

VITAMIN D

This vitamin controls the deposition of calcium and phosphorus in bones and teeth. In its absence the disease known as rickets (rachitis) develops. Mellanby[462] showed that cod liver oil, butter, and fat have a marked antirachitic action. Since these substances also contain vitamin A it was first thought that this vitamin possesses the antirachitic action. However, when McCollum and his associates[459] found that cod liver oil, after oxidation, no longer shows typical vitamin A activity but retains its antirachitic power it was concluded that the two effects depend on two separate factors.

Fig. 300.

Fig. 301.

Fig. 300.—Photograph of two puppies after being fed for eighteen weeks after weaning on the same diet, deficient in vitamins A and D. Puppy 1 (left) was the offspring of a mother fed during pregnancy and lactation on a diet rich in vitamins A and D and containing bread as the cereal, whereas the mother of puppy 2 (right) was fed on a diet deficient in these vitamins and having oatmeal as the cereal. It will be noted that puppy 1 shows little sign of rickets, while puppy 2 has developed severe rickets. (Reproduced by permission of Controller of H. M. Stationary Office from Med. Res. Council Report No. 167.)

Fig. 301.—Rickets following a diet of 175 ml. of whole milk, white bread ad lib., and 10 ml. of linseed oil per day. Time of experiment, 5½ months. Increase in weight during period of experiment 2,670 Gm. (Reproduced by permission of Controller of H. M. Stationery Office from Med. Res. Council Report No. 167.)

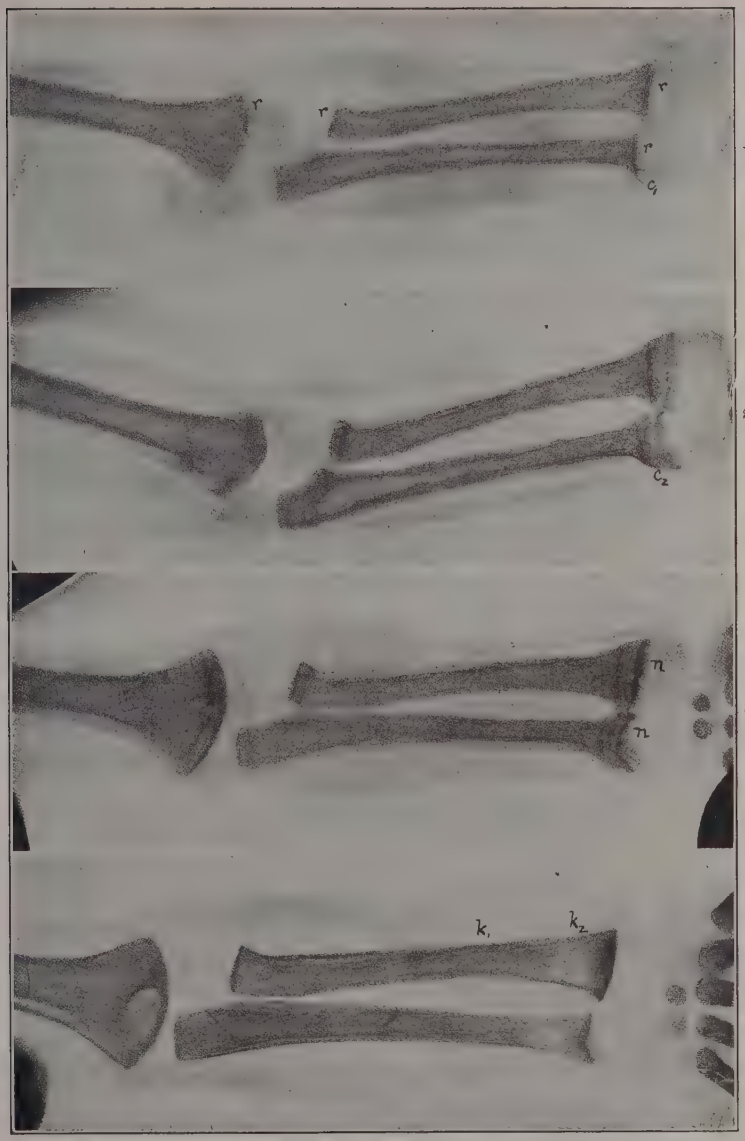


Fig. 302.—X-ray photographs illustrating severe rickets in a child of ten months and recovery after treatment with cod liver oil. (Reproduced by permission of Controller of H. M. Stationery Office from Med. Res. Council Report No. 167.)

1. March 10, 1922. Florid rickets, osteoperosis. Structure of bones coarse, metaphyseal margins (r) frayed. Distal end of ulna slightly cupped, uncalcified osteoid zone at C_1.

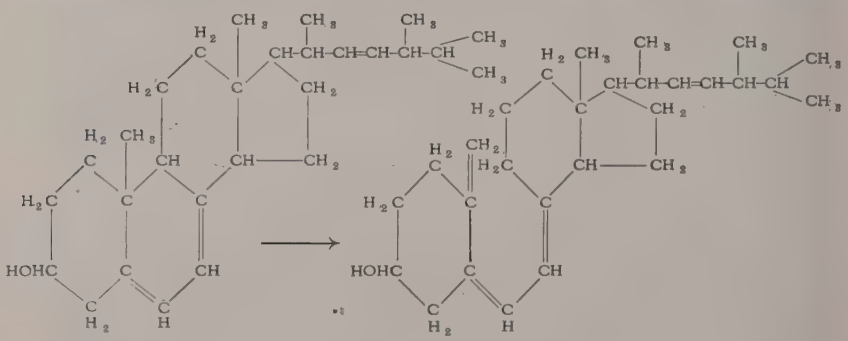
2. April 4, 1922. Healing in progress after twenty-seven days' treatment. Calcium depositing along the shafts, at metaphyseal margins and at C_2.

3. April 11, 1922. Rapid progress. Dense calcification at n; increase in periosteal calcification; calcification of center of ossification at distal end of humerus.

4. June 15, 1922. After three months' treatment. Contour of shafts nearly normal, bone finely meshed. Fine homogeneous new bone (k_2) distinguishable from k_1, formed before onset of rickets.

The diagnosis of rickets rests on the following: Clinical examination shows that the bones are deformed (Figs. 300 and 301); there is beading of the costochondral junctions and enlargement of the epiphyses. It is difficult, however, from clinical examination alone to decide whether the process is an active one, and in its earliest stages the disease defies ordinary methods of examination. Therefore the radiographic method must be employed. The photographs reproduced in Fig. 302 show different stages of rickets in the dog. Histological examination demonstrates the presence of uncalcified osteoid tissue which accumulates at the epiphyses in amounts varying with the intensity and duration of the disease.

Chemistry of Vitamin D.—Huldschinsky[454] in 1919, discovered that infantile rickets can be cured by exposure to ultraviolet radiation. Later, Hess and Unger[450] found that sunlight has the same curative effect. The next step in advance was that of Hess and Weinstock[451] who demonstrated definitely that food deficient in vitamin D develops anti-rachitic properties when it is exposed to ultraviolet light. It was thought at first that cholesterol is the material involved in the change. Rosenheim and Webster[468] demonstrated, however, that the provitamin activity is possessed by an impurity carried down with the cholesterol. This substance was identified as ergosterol. Rosenheim and Webster found that as little as 0.0001 mg. of irradiated ergosterol per day prevents rickets in rats. The next step in the development of this subject was the isolation of a crystalline antirachitic substance from solutions of irradiated ergosterol. Askew and his associates,[420] using distillation in a high vacuum, obtained "calciferol" which represents vitamin D in a high state of purity. The



ergosterol

calciferol (vitamin D)
(Windaus)

chemical changes which take place in the molecule on irradiation include a rupture of the central ring of the phenanthrene nucleus and a formation of a methylene group at C_{18} in place of the original methyl group.

Several substances may act as provitamins which, on radiation, develop vitamin D activity. In fact, ten forms of vitamin D are known, but only two are of practical importance: the activated ergosterol of plant origin (calciferol) and the activated 7-dehydrocholesterol of animal origin. The experimental activation of a cholesterol of animal origin explains the curative effect of sunlight in human cases of rickets.

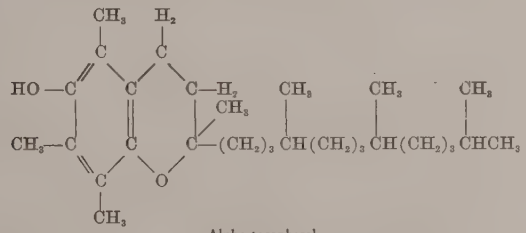
VITAMIN E

Proof of the existence of this vitamin has been more difficult to obtain than in the case of vitamins A or D. It was particularly from the work of Mattill and Conklin[461] and of Evans[433] that its existence was made probable. It was found that although rats fed on a milk diet do not breed normally, their reproductive functions are restored when lettuce, wheat germ, or yeast is added.

In the female rat, vitamin E deficiency leads to interference with the nutrition of the fetus so that it atrophies and is absorbed. If food containing this vitamin is given from the fifth to the nineteenth day after mating, the pregnancy will proceed to a successful issue, even though the diet preceding this period was deficient. In male animals, continued absence of vitamin E leads to incurable atrophy of the germinal epithelium of the testes.

Following the discovery of this vitamin, it was successfully applied to the cure of abortion in human cases.

Chemistry of Vitamin E.—This vitamin is unaffected by heat, light, acids, and alkalies. It occurs in the nonsaponifiable fraction of wheat germ oil. Evans, Evans, and Emerson[433] have isolated an alcohol which possesses vitamin E properties. Vitamin E has been purified and its structure established. It is an alpha-tocopherol and has the following structure (Karrn et al.;[455] Fernholz;[437] Smith et al.[474]):



Alpha-tocopherol

The natural sources of this vitamin are cereals, lettuce, bananas, milk, eggs, and muscles.

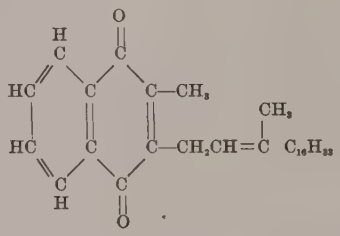
ESSENTIAL FATTY ACIDS

Burr and his associates[422, 423] have demonstrated the importance of some of the unsaturated fatty acids in nutrition. Feeding rats a purified diet of casein, sucrose, salt mixture, and vitamins A, D, and E, they discovered that these animals did not gain their full weight and developed a scaly condition of the skin, especially of the tail. This is cured and normal growth attained when small amounts of linoleic acid are added to the diet. Evans and Lepkovsky[434] have confirmed the observations of Burr that the essential substances are unsaturated fatty acids. Apparently, the animal body is unable to desaturate fatty acids to form these essential unsaturated acids or to make them synthetically.

VITAMIN K

The term vitamin K was proposed by Dam[428] to describe the substance (Koagulations Vitamin) necessary to prevent a hemorrhagic disease in chicks. This disease in chicks is characterized by a delayed clotting time and the ap-

pearance of hemorrhage. The delayed clotting time is associated with a low prothrombin content. The vitamin is a fat-soluble nonsterol portion of an ether extract of alfalfa. This vitamin has been prepared in pure form. The formula given to this vitamin is:



A detailed description of this vitamin and its use in blood coagulation studies is given in Chapter XXVIII.

CHAPTER LVII

NUTRITION: FOOD REQUIREMENTS AND INORGANIC SALTS

Burnet and Aykroyd[491] have described nutrition as an economic, agricultural, industrial and commercial problem, as well as a problem of physiology. Psychology may be added to the list since the sensation of taste and certain conditioned responses (see Chapters XXVI and XX) play important roles in nutrition. For the student of human physiology the subject of nutrition may be limited to a study of the nutritive requirements of man. These requirements are those of protein, carbohydrate, fat, calories, minerals, and vitamins. Nutrition, therefore, includes a study of the energy metabolism of man, because it is through such studies that the caloric requirement is determined. Thus such problems as the specific dynamic action of foodstuffs, the metabolism during exercise and the reaction of the metabolism of man to external temperature are parts of the subject matter of nutrition. In fact, this section (Part V) of the book is called "Metabolism and Nutrition." Two subjects which have not been discussed in the preceding chapters, namely, the caloric requirement of man and the need of inorganic ions, may conveniently be made the subject of a separate chapter.

Food Requirements

The latest study of the theoretical food requirements of man has been made by a Commission appointed by the Health Committee of the League of Nations.[491] The conclusions reached by this Committee are presented below:

1. **Caloric Requirements.**—Twenty-four hundred Calories per day are considered adequate for an adult living in a temperate climate and not engaged in manual work. To this basic requirement the following supplements should be added for muscular activity:

Light work:	50 Calories per hour of work.
Moderate work:	50-100 Calories per hour of work.
Hard work:	100-200 Calories per hour of work.
Very hard work:	200 Calories and upwards per hour of work.

The energy requirements of children and mothers are indicated in Table LXXXV.

TABLE LXXXV

AGE (YEARS)	COEFFICIENT OF NORMAL REQUIREMENT	CALORIES
1-2	0.2	720
2-3	0.4	960
3-5	0.5	1200
5-7	0.6	1440
7-9	0.7	1680
9-11	0.8	1920
11-12	0.9	2160
12 and upwards	1.0	2400
Women:		
Pregnant	1.0	2400
Nursing	1.25	3000

2. **Protein Requirements.**—The daily protein intake for all adults should not fall below one gram per kilogram of body weight. The protein should be

derived from a variety of sources and part of the protein should be of animal origin. During pregnancy and lactation some animal protein is essential, and in the growth period it should form a large proportion of the total protein. The required amounts are indicated in Table LXXXVI.

3. **Fat Requirements.**—Fat must be a constituent of a normal diet, but the data at present do not suffice to permit a precise statement of the quantity required.

TABLE LXXXVI

AGE (YEARS)	GRAMS OF PROTEIN PER KILOGRAM BODY WEIGHT
1-3	3.5
3-5	3.0
5-15	2.5
15-17	2.0
17-21	1.5
21 and upward	1.0
Women:	
Pregnant	2.0
Nursing	2.0

4. **Mineral and Vitamin Requirements.**—The Commission recognized the fact that the deficiencies of modern diets are usually in the protective rather than in the strictly energy-bearing foods. Among the former are, first and most important, milk and milk products, eggs and glandular tissues, then, green leaf vegetables, fruits, fat, fish, and meat. Among the energy-bearing foods of little or no protective power are sugar, milled cereals and certain fats. Refined sugar is entirely devoid of minerals and vitamins. The increasing habit of consuming large amounts of sugar tends to lessen the quantity of protective foods in the diet and is to be regarded with concern.

5. **Requirements of Pregnancy and Lactation.**—The Commission also attempted to define the quantity of protective foods necessary for perfect nutrition in terms of the requirements of the pregnant or nursing woman. She should be regarded as the member of the population needing the greatest "protection" in order to ensure adequate physical endowment for the child at birth and optimum nutrition during infancy. From a study of specimen diets, the Commission drew up the accompanying table (Table LXXXVII) which contains what is considered adequate for a nursing or pregnant woman.

This Commission also drew up the following general recommendations:

A. It is a general principle that a varied diet tends to safety, provided it contains a sufficiency of the protective types of food materials.

B. White flour in the process of milling is deprived of important nutritive elements.

C. The consumption of an excessive amount of sugar is to be condemned, and in this case partial replacement by potatoes is urged.

D. Milk should form a conspicuous element in the diet at all ages.

E. Fresh vegetables and fruit should always be constituents of the normal mixed diet.

F. Extra vitamin D, either as cod liver oil or as irradiated products, should be given whenever sunshine is not abundant, especially in the period of growth and during pregnancy.

The question now arises as to the actual quantities of these foodstuffs taken by the average person. The majority of people in civilized countries obtain sufficient food for energy purposes and adequate protein. Information concerning food consumption has been obtained by making a house-to-house study of certain districts. For example, Cathcart and Murray[492] investigated the diets of 154 families of St. Andrews, Scotland. They found that individual members of these families were ingesting 83.8 grams of protein, 118.6 grams of fat, and 410.7 grams of carbohydrate a day. The energy value of this diet was 3,119 Calories. According to the standards set by the Commission of the League of Nations such a diet is adequate as regards calories and protein. Unfortunately, similar studies were not made on the vitamin and mineral contents of the food of this group.

TABLE LXXXVII

DIETARY SCHEDULE FOR THE PREGNANT AND NURSING WOMAN

FOOD	AMOUNT (GRAMS)	CALCIUM (GRAMS)	PHOSPHORUS (GRAMS)	IRON MG.	IODINE MG.	VITAMINS					CALORIES
						A INTERNATIONAL UNITS	B_1	B_2	C INTERNATIONAL UNITS	D	
A. Protective Foods:											
Milk	1000	1.2	0.9	2.4	0.02-0.05	3000	50	Rich	Poor	Poor	660
Meat	120	–	0.3	3.0		Poor	Poor	Rich	Poor	None	260
Eggs	50	–	0.1	1.4		1,300	14	Rich	None	40	70
Cheese	30	0.3	0.2	0.4		800	Poor	Good	Poor	Poor	125
Green vegetables	100	0.5	–	1.0		100	25	Good	300	None	30
Potatoes	250	–	0.2	3.0		Poor	50	Good	320	None	250
Legumes (dried)	10	–	–	2.0		Poor	15	Good	None	None	35
Cod liver oil	3.5	–	–	–	Richest source	3,500	None	None	None	300	30
Raw fruits or vegetables for vitamin C	–										
B. Energy-Yielding Foods:											
Cereals	250	–	0.2	3.0							1,000
Fats and sugar	as needed										

Undernutrition.—The fact that there are individuals in this country living on a restricted diet shows that even in a well-organized social system, undernourishment is present. In certain poorly organized systems, the majority of individuals are not only undernourished, but are continually threatened with famine. For example, a folk saying in Russia, "May God grant us an increase of our cattle and many child deaths," arises from the many famines that have occurred in that country. In recent years, Russia has had famines (in 1891, 1906, 1911, 1920-1922 and 1931-1932) in which millions have starved. Ireland, India, and China also have had many famines. In fact, man's history has been largely a struggle for food. In this respect historical accounts are often er-

roneous, for they seldom describe the amount of food available to the common man but merely relate the banquets of the nobles. Indeed, it has been stated that it was not until the end of the eighteenth century that man began to escape from the sole aim of obtaining sufficient food. Even now, man lives on a narrow margin. Four years of war and several revolutions in Germany produced the results shown in Table LXXXIX. Five years later matters were even worse. Obviously these conditions are of great physiological interest, and important information results from studies on large numbers of individuals suffering from starvation.

Starvation may be acute or chronic, and may be subdivided into several types. For example, one may speak of oxygen starvation or anoxia, fat starvation resulting from lack of fat in the diet, water starvation from lack of water, and vitamin starvation from vitamin deficiency. In fact, man can starve for lack of any of the essential food materials. However, the term generally implies *caloric starvation.*

Acute Caloric Starvation.—Man has gone for as long as fifty days without food. The most thorough study of the effect of acute starvation is that of Benedict.[490] A summary of his results is given in Table LXXXVIII. It may be seen from this table that with the decrease in weight, there is a decrease in total metabolism. The body conserves salts by decreasing the output of sodium and chloride. The subject was in ketosis, as may be seen from the output of β-hydroxybutyric acid. Hemoglobin concentration of the blood was maintained at a normal level. There was a slight fall in body temperature and pulse rate. These are the major effects of acute starvation.

TABLE LXXXVIII

THE PHYSIOLOGICAL AND BIOCHEMICAL CHANGES DURING FASTING (BENEDICT[490])

DAYS OF FASTING	1	11	21	31
Body weight, kg.	59.60	53.88	50.49	47.39
Rectal temp.	——	36.54	36.04	35.96
Pulse rate	74.0	61.0	59.0	60.0
Hemoglobin	90.0	85.0	88.0	92.0
Alveolar CO_2T, mm. Hg	32.8	——	28.7	31.8
Urine (wt. in grams)				
Total N	7.10	10.25	7.93	6.94
Urea N	5.68	7.66	5.54	4.84
Chloride	3.77	0.36	0.18	0.13
P_2O_5	1.66	1.95	1.60	1.32
S	0.46	0.62	0.51	0.49
β-hydroxybutyric acid	——	0.14	5.0	4.5
Na	2.070	0.100	0.066	0.053
O_2 ml. per min.	212.0	176.0	154.0	160.0
Cal. per sq. meter body surface per 24 hours	843.0	732.0	653.0	701.0

Chronic Caloric Starvation.—In Germany at the start of the war of 1914-1918, a committee determined that the population could exist without serious disturbances on the diet of 1,985 calories given in Table LXXXIX. For many reasons, however, the people never obtained this diet but were given one containing only 1,344 calories per day. Naturally, chronic starvation afflicted most of the population. The physiological changes are of interest (von Muller,[498] Lusk[495]). In the first place, there was marked loss of weight, and with this loss of weight there was a decrease in diseases associated either directly or indirectly

TABLE LXXXIX

DIET PER CAPITA PER DAY FOR WINTER OF 1916-1917 IN GERMANY (LUSK[495])

	AS PLANNED			AS PROVIDED		
	AMOUNT GRAMS	PROTEIN GRAMS	CALORIES	AMOUNT GRAMS	PROTEIN GRAMS	CALORIES
Bread	271.0	17.2	688	271.0	17.2	688
Potatoes	710.0	14.9	710	357.0	7.5	341
Butter and margarine	18.0	—	140	11.4	—	89
Milk	200.0	6.8	111	—	—	—
Meat	70.0	10.7	158	36.0	4.5	78
Eggs (per piece)	0.3	4.2	53	0.07	1.0	13
Sugar	32.0	—	125	26.0	—	104
Cereals	—	—	—	9.8	0.9	31
Totals	—	53.8	1,985	—	31.1	1,344

with overeating (gout, nephritis, and diabetes). There was also a lowering in basal metabolic rate. This shows an interesting adaptation on the part of the body, since the decrease was relatively greater than the loss of weight. In such cases, therefore, the body is compensating for the decreased intake by a decrease in output of energy. In cases of long continued starvation edema, gangrene around the mouth (noma), and osteomalacia developed. The edema may have been due to lack of blood proteins and the osteomalacia to lack of vitamins.

There were also marked psychological changes: depression and disinclination to work or play. In fact, every movement was reduced as far as possible to meet the reduction in caloric intake. Serious social changes, even cannibalism, have resulted from chronic starvation. Gantt[493] has described such a condition in Russia during a recent famine. It is little realized that our modern development rests on an adequate supply of food and that as soon as this becomes inadequate, man reverts to a lower form of society.

Obesity.—It is commonly recognized that there are two types of obese individuals: the overeating-underexercising type and the endocrine or constitutional type. The majority of cases of obesity are of the first type, as was demonstrated in Germany during the war of 1914-1918. For, as the report above shows, after several years of chronic starvation there were no obese individuals in that country. It is surprisingly easy to ingest more calories than needed. When one considers that a small piece of butter weighing 14 grams yields 100 calories and the maximal daily requirement is about 3,000 for moderate work, it is easy to understand how most individuals have a positive caloric balance and gain weight. Tables showing the normal weights for the various heights have been constructed, and the use of such tables gives an index of treatment. The standards used by the Army Air Corps are given in Table XC (Armstrong[489]).

The treatment of the most common type of obesity is obvious but difficult. Caloric intake should be reduced, and the amount of exercise increased. It has been calculated that, walking at the rate of five miles an hour, it would be necessary to cover a distance of 34.75 miles to rid the body of one pound of fat. The additional difficulty is that exercise increases appetite, which, if satisfied by extra food, soon counteracts the effect of exercise. The more rational treatment is a gradual reduction of food intake. A factor which must be considered in such reduction is the retention of water. Newburgh and Johnston[499] noted

TABLE XC

STANDARDS OF HEIGHT AND WEIGHT (ARMSTRONG[489])

HEIGHT	WEIGHT ACCORDING TO AGE PERIOD			
INCHES	20-25		26-30	
	STANDARD	MINIMUM	STANDARD	MINIMUM
64	128	115	131	116
66	136	121	139	124
68	144	129	147	132
70	152	137	155	140
72	160	145	164	149
74	168	153	174	159
76	176	161	184	169
78	184	169	194	179

that a patient weighing 231 pounds lost no weight for several days after being placed on a starvation diet. In fact, it was thirteen days before the actual weight reached the expected level. Water balance studies in this individual demonstrated that the difference was due to water retention during the early part of the starvation period. Therefore, loss of body fat may be masked by water retention.

Adiposity may be produced by abnormalities in the function of the thyroid, pituitary, and sex glands. This type of obesity may result secondarily from overeating. The primary change in the hormonal control may affect the individual so that the normal ratio between needs of the body and caloric intake may be disturbed, with the result that the patient overeats.

The Role of Inorganic Salts in Animal Nutrition

Inorganic salts are just as necessary as organic foodstuffs for the maintenance of life. The absence in the diet of those needed in the smallest traces is just as incompatible with life as is the absence of those that are required in abundance. In fact, certain of the elements ingested in the food material play such a prominent role in the regulation of metabolism that they may be looked upon as inorganic vitamins.

The inorganic salts may be divided into two groups. The first are those that are needed in relatively large quantities to supply the important ions of the body for the maintenance of normal osmotic pressure, to regulate the hydrogen ion concentration, or to provide structural materials. The second are those that are needed in small quantities and act as regulators of metabolism. The latter group, the inorganic vitamins, are called "trace" elements. In the first group are the chlorides, phosphates, and sulfates which form the anions of the body fluids, as well as sodium, potassium, calcium, and magnesium which form the positive ions or cations. Some of these elements, like calcium, are used for structural purposes. Iron and iodine must be included in this group, for they enter into the structure of hemins and thyroxin, respectively. In the second group are a large number of elements such as aluminum, bromine, cobalt, copper, iron, manganese, nickel, zinc. The functions of this class are not as well defined as those of the first group since their roles are revealed only by deficiencies or excesses of the elements in a diet. Many other elements have been shown to be present by spectroscopic analyses of ash from the animal body.

Whether these are essential in animal metabolism or merely contaminants from the utilization of vegetable food material is not known.

Inorganic Salt Content of Foods.—In the case of man, the inorganic salts, with the exception of sodium chloride, are contained usually in adequate quantities in the natural foodstuffs. However, animals fed and developed for the production of food may need the addition of minerals to their diets for successful nutrition. The quantity of inorganic salts obtained with natural foodstuffs varies tremendously. Some foods, such as white flour, sugar, and cornstarch, contain practically no mineral elements, while milk, green vegetables, and meat are rich in these materials. The inorganic salt content of some of the commoner foodstuffs is given in Table XCI. Recent dietetic surveys have

TABLE XCI

CONTENT PER 100 GM.* OF THE MORE IMPORTANT MINERALS OF CERTAIN FOODS IN THE FRESH STATE

(Compiled from Sherman's tables.)

FOOD	CALCIUM MG.	PHOSPHORUS MG.	IRON MG.	SODIUM MG.	POTASSIUM MG.
Beef (lean)	0.007	0.218	3.0	0.084	0.338
Eggs	0.067	0.180	3.0	0.143	0.140
Milk	0.120	0.093	0.24	0.051	0.143
Cheese	0.931	0.683	1.3	0.606	0.089
Wheat flour	0.020	0.092	1.0	0.060	0.115
Rice, polished	0.009	0.096	0.9	0.025	0.070
Oatmeal	0.069	0.392	3.8	0.062	0.344
Cabbage	0.045	–	1.1	0.027	0.247
Carrots	0.056	0.046	0.6	0.101	0.287
Potatoes	0.014	0.055	1.3	0.021	0.429
Apples	0.007	0.012	0.3	0.011	0.127
Oranges	0.045	0.021	0.2	0.012	0.177
Prunes (dried)	0.054	0.105	3.0	0.069	1.030
Watercress	0.187 (?)	0.005	1.9	0.099	0.287

*It is obvious that these values will vary considerably for most of the foods. For instance, in the meats they will depend on the amount of fat (which is nearly salt-free), and in vegetables with the mineral content of the soil upon which they are grown. When any degree of exactitude is required, as in making surveys of the mineral content of dietaries in a community, it is necessary that several of the available foodstuffs be subjected to special analysis.

shown that the danger of an adequacy in inorganic salt consumption is not frequently incurred, especially among the members of the poorer classes living in large cities, who consume large quantities of bread but inadequate amounts of milk, eggs, green vegetables, and meats. The function of some of the more important inorganic elements will now be separately considered.

Sodium and Potassium.—Both of these elements occur as chlorides, phosphates, and carbonates and in combination with simple organic acids, such as hydroxybutyric or lactic, and with the carboxyl group in large molecules of proteins and other complex compounds. Sodium is the chief cation of the body fluids, while potassium is found chiefly in the cells (see Chapter LXXVIII). Sodium chloride is responsible for maintaining the correct osmotic pressure of the body fluids, although other soluble constituents aid in its regulation. It is excreted constantly, chiefly in the urine. In order to maintain its store in the organism, fresh supplies, amounting to nearly two grams a day, must be taken with the food. During prolonged fasting, the excretion may become very low; for example, it fell to 0.13 grams per day in the fasting man studied by Bene-

diet (page 834). St. John[527] found that amounts of sodium below 0.3 per cent of the total food intake were inadequate for growth in rats. The ordinary intake of plant and animal tissues contains an abundant supply of potassium. Experimentally, Miller[522] has shown that rats fail to grow and eventually die when the daily intake of potassium is 1.0 mg. or less. For normal growth, male rats require as much as 15 mg. per day, while females require only 8 mg.

Calcium.—In the blood of adult human beings, the calcium concentration is maintained at 10 mg. per 100 ml. of blood. This calcium level represents a balance between absorption from the intestine, excretion in the feces and urine, and deposition in the bones and teeth. The parathyroid glands control calcium metabolism; removal of these glands causes the blood calcium to fall and, if extracts of the parathyroid glands are injected, the calcium content rises. According to Peters and Van Slyke,[506] the normal serum calcium may be considered to be made up of: a small portion held in solution by forces which govern solubility in salt solutions; a portion held in solution by serum proteins; and a portion which remains in solution either by virtue of the retarded precipitation that is characteristic of supersaturated solutions of calcium carbonate and phosphate or by the formation of complexes.

A decrease in calcium ions or an increase in potassium ion causes an augmentation of irritability not only in the heart muscles but also in skeletal muscle. In fact, if these changes are pronounced, tetany develops. Shohl[509] has classified the types of tetany in the manner shown in Table XCII.

TABLE XCII

TYPES OF TETANY (SHOHL[509])

	Ca	Ca^{++}	PO_4	CO_2	pH
1. Low calcium					
Rachitic	low	low	high	normal	normal
Low calcium intake	low	low	high	normal	normal
Parathyroid	low	low	high	normal	normal
2. High phosphate	low	low	high	normal	normal or elevated
3. High bicarbonate	normal	?	?	high	elevated
4. Hyperventilation	normal	?	normal	normal	elevated
5. Citrate	high	low	normal (?)	normal	normal
6. Low magnesium	normal	normal	normal	normal	normal

An interesting biological approach to this problem was made by McLean and Hastings[520, 521] who used the amplitude of heat of the frog's heart to determine the concentration of calcium. From this work it became clear that the protein of the serum is the main factor in the ionization of calcium. The dissociation constant may be determined by

$$\frac{[Ca^{++}] \times [protein^{--}]}{[Calcium\ proteinate]} = K$$

or conversely $[Ca^{++}]$ may be calculated from the combination of total calcium and protein. The value of K is given as $10^{-2.22}$. In addition to these physiological functions, calcium is preeminently the skeletal element of the body and plays a role in the clotting process. The calcium requirement for man averages about 0.45 gram per day (Sherman[500]).

Phosphorus.—The physiological importance of this substance in the animal is indicated by its widespread presence in many parts of the organism and in its many physiological uses. It is present in large amounts in the bones and forms, in the blood, monobasic and dibasic salts which are of importance as buffer substances. Compounds of phosphoric acid with organic radicals are very common, for example, the phospholipids which are present in nearly all tissues. United with purine bases, phosphoric acid enters into the structure of nucleic acids and, in muscle, unites with creatine to form phosphocreatine. The combination of phosphoric acid with hexoses is a very important intermediate compound in carbohydrate metabolism. Deficiency of phosphorus in a young animal produces rickets. The deposition of calcium and phosphorus in the bones appears to depend not so much on the absolute concentration of either in the blood as on the proportion between the two. Therefore, any change in the amount of phosphorus in the blood must be correlated with the concentration of calcium.

Recent interest in phosphorus metabolism has resulted from the introduction of radioactive phosphorus. This isotope (see page 723) which has a half life of 14.8 days, is easily prepared and detected. Cohn and Greenberg[511] studied the rate at which different organs absorb phosphorus. They found that heart, kidney, and liver absorb phosphorus very quickly. Hahn, Hevesy and Lundsgaard[513] have found that radioactive phosphorus remains in the body about thirty days.

Phosphorus is an essential in the diet. Osborne and Mendel[525] have demonstrated that rats do not grow on a phosphorus-deficient diet. Sherman[500] states that 0.88 gram of phosphorus per day is the minimal amount for a positive balance in a man of average weight.

Iron.—Iron enters into the formation of hemoglobin and of certain tissue pigments. An adult man requires in his food about 15 mg. of iron per day. Iron is absorbed through the duodenum in the ferrous form and is excreted by the large intestine and cecum. It is stored in the liver. The study of the metabolism of iron has been aided by the use of a radioactive isotope of this substance. Whipple and his associates[514] have demonstrated that the amount of radioactive iron that is absorbed depends on the need of the body for iron. Radioactive iron was found inside the red blood cells three hours after ingestion. Small amounts were also detected in the liver and bone marrow.

Sherman[500] states that 15 mg. a day may be considered the standard allowance. It is very difficult, however, to make exact balance studies with iron salts, because iron is held in storage in the body for a long time after ingestion.

A very interesting synergism between iron and copper is brought out in the cure of the anemia which results from a diet deficient in these elements. Hart and his associates[517] have shown that purified iron salts fed to rats on a milk diet are ineffective in stopping the progressive anemia. If the iron is fed as an ash of lettuce, yellow corn, or beef liver, the hemoglobin level is restored to its normal value. It was found that this restoration depends on the presence of a trace of copper. The exact role played by copper in the formation of hemoglobin is not known. It does not enter into the molecule but may act as a catalyzer of some of the intermediate reactions in hemoglobin formation. The common natural sources for iron are liver, kidney, eggs, fish, oysters, spinach, and oatmeal.

Iodine.—Iodine is present in minute traces in all of the tissues. It is present, however, in large amounts only in the thyroid gland where it becomes an

integral part of thyroxin. Goiter develops in individuals receiving insufficient amounts of iodine. Sea foods are rich in iodine; oysters especially contain a large amount of this substance.

Radioactive iodine has recently been used in metabolism studies. Hamilton[515] has found that this substance is absorbed very quickly. It may be detected in the body within three to six minutes after ingestion, and absorption is complete in three hours. In a later study, Hamilton and Soley[516] demonstrated that the thyroid gland in patients suffering from goiter takes up radioactive iodine.

Magnesium.—In the plant world, magnesium occupies the important place which iron holds in the animal kingdom, for magnesium is as essential an inorganic element in the chlorophyll molecule as iron is in the hemoglobin molecule. Its exact function in the animal body is not completely understood. It does enter into the composition of bone and may replace calcium in that structure. It is present in blood. Magnesium also plays a role as a coenzyme in glycolytic systems (Chapter XLVIII).

Magnesium is essential to the life of an animal. McCollum and his associates[519] have shown that electrical stimulation of rats on low magnesium diets resulted in spontaneous convulsions and tetany. Sherman[500] states that the average American diet contains about 0.27 gram a day. This is sufficient for a positive balance since it has been demonstrated by Tibbets and Aub[526] that 0.22 gram was adequate.

Borsook and his associates[519] have studied the metabolism of sulfur with a radioactive isotope. Following the feeding of 202 mg. of this form, 15 per cent appeared in the urine in the first nine-hour period after ingestion, and 32 per cent in the period from nine to twenty-four hours after ingestion. Therefore, only 47 per cent of the radioactive sulfur was excreted. These authors conclude that there is continuous exchange of sulfur in the tissues.

Other Inorganic Elements.—In this group are manganese, fluorine, copper, bromine, nickel, and zinc. Orent and McCollum[523] have shown that manganese is essential to the rat. On a manganese-free diet, the males underwent testicular degeneration, and the females lost interest in their young and did not give them an opportunity to suckle. The chief sources of manganese are milk, bran, and nuts. Everson and Daniels[512] state that children should have from 0.2 to 0.3 mg. per kilogram of body weight per day.

The quantity of fluorine ingested is of importance, because overdoses produce chronic poisoning. In rats, the symptoms of this condition are brittle and opaque teeth, and, in human subjects, a mottling of the enamel. This condition appears in regions in which there is more than 2.5 mg. of fluorine per liter of drinking water.

Cobalt, copper, and zinc are also essential. The important role of copper in the formation of hemoglobin is discussed in the section on iron. An excess of cobalt, fed in combination with copper, produces polycythemia in rats (Orten et al.[524]). Zinc is also essential for life (Howe et al.[578]). This element is found in large concentrations in the pancreas and it aids in the *in vitro* crystallization of insulin.

CHAPTER LVIII

THE PHYSIOLOGY OF MUSCULAR EXERCISE

During muscular exercise, the increased demand for oxygen by the active muscles and the need for carrying away the waste products of metabolism from the muscles bring into action many of the systems of the body. Therefore, the physiology of muscular exercise illustrates the correlation of the functions of the respiratory, nervous, muscular, and other systems and demonstrates how the various organs adapt themselves to the tremendous demands placed on them during muscular work. These adaptations are important not only as a physiological study but also as a practical basis for the measurement of man's ability to produce useful work. A thorough knowledge of this subject enables a physician to evaluate the ability of a patient to work. This is important to a doctor, as the first question asked him by a recovering patient is usually, "When may I get up and go back to work?"

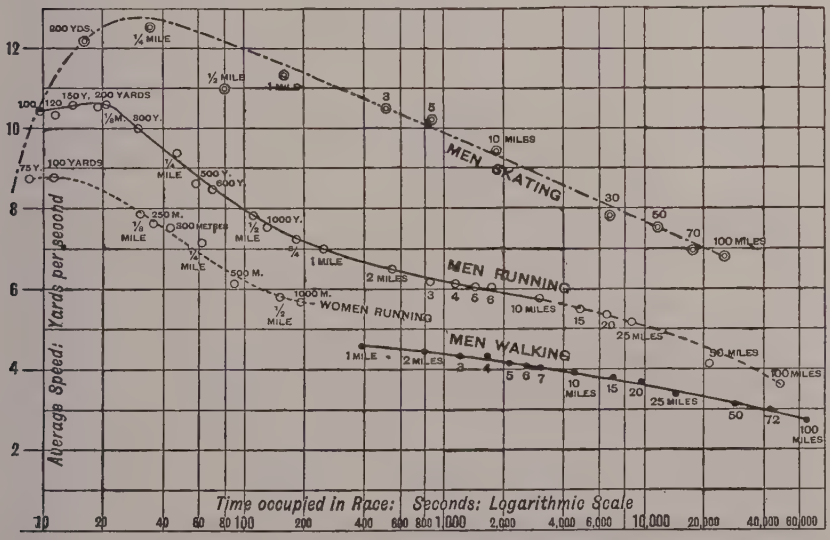


Fig. 303.—Relationship between speed and total time occupied in race. (From A. V. Hill: Living Machinery, New York, 1927, Harcourt Brace and Company.)

Man and animals have developed adaptations for exertion to a remarkable degree. Athletes have been able to propel themselves 100 yards in less than ten seconds and have been able to walk 100 miles in twenty-one hours and thirty-six minutes. These records are remarkable demonstrations of speed and endurance. The times for running various distances by man are given in Fig. 303. These curves illustrate that there is a definite relationship between speed and duration of endeavor. It is the purpose of this chapter to discuss

the adaptations of man to exercise and to define the limiting factors governing the ability of man to carry out muscular endeavor. Not all of this information covering the interactions of the various systems has been obtained under conditions of muscular exercise in man. Many types of animal experimentation have contributed to this knowledge. It is reasonable to suppose that certain mechanisms, such as the Bainbridge reflex (see page 469), which has been shown to go into action in the resting anesthetized animal, will also operate in the intact working animal. Therefore, results from such experiments may be applied to man. The final decision, however, must await results obtained in experiments made on the exercising animal or on man.

RESPIRATORY METABOLISM

The fundamental change during muscular exercise is the increased metabolism of the skeletal muscles. This involves a greatly augmented consumption of oxygen, the quantity used depending on the amount of work (Fig. 304).

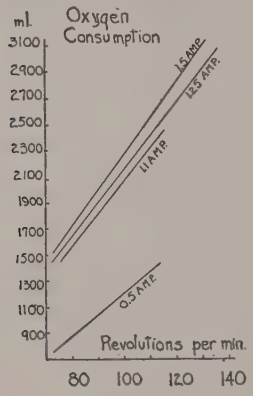


Fig. 304.

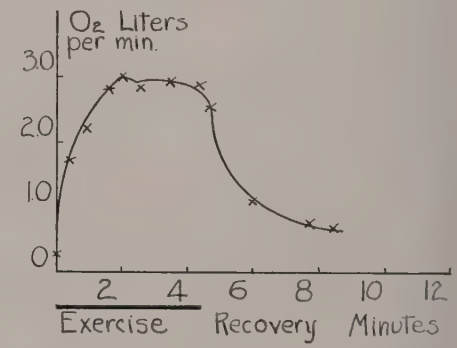


Fig. 305.

Fig. 304.—Relationship between the oxygen consumption and the amount of work done (revolutions of bicycle wheel per minute with subject pedalling with different loads). (From Benedict and Cathcart: Carnegie Inst. of Washington, Publ. No. 187, 1913.)

Fig. 305.—Oxygen consumption during and after exercise. (Redrawn from Furusawa: Proc. Roy. Soc. B. 99: 148, 1926.)

In the chapter on The Chemistry of Muscular Contraction (Chapter LII) a description was given of the utilization of oxygen by isolated muscle during and following stimulation. In these preparations it was found that there are two phases of the augmented oxygen consumption; the one occurs during the muscular contraction and the other after the contraction. Similar results are obtained when the oxygen consumption is measured in man during and after muscular exertion (Fig. 305). The phase occurring during muscular exertion may be subdivided into two parts, the initial rise and the "steady state." The fact that the metabolism does not rise immediately to the final plateau indicates that there is a slight lag in the circulatory and respiratory adjustments at the beginning of exercise. The plateau is soon reached, and this part of the curve is called the "steady state." It may be defined as the condition in which the intake of oxygen meets the metabolic needs of the muscle. On this

plateau, the respiratory and circulatory adjustments are sufficient to meet the need. Under the condition of light muscular exercise, the recovery period is of short duration and of such magnitude as to compensate for the lag in oxygen intake at the start of the experiment.

These facts apply only to moderate muscular exercise, because, if the severity of the exercise is increased, a point is reached where the intake of oxygen no longer keeps pace with the metabolic needs. At this point, the relationship between the oxygen requirement for work and the intake of oxygen changes (Fig. 306). Therefore, the first limiting factor is the maximal amount of oxygen that an individual may take in per minute. This is conditioned by the efficiency of the respiratory and circulatory systems. Generally it is about 4.0 liters per minute but values as high as 5.1 have been recorded (Robinson, Edwards and Dill[601]).

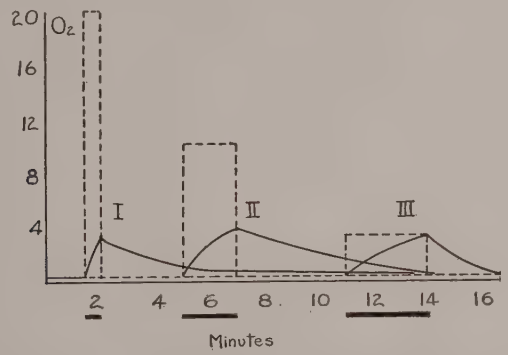


Fig. 306.—Diagram illustrating the difference between the oxygen requirement and the oxygen intake. Areas under broken lines: oxygen requirement in liters. Areas under solid lines: oxygen intake in liters. I, severe exercise; II, moderate exercise; III, light exercise. Duration of work given by heavy black lines. (From Furusawa, Hill, Long and Lupton: Proc. Roy. Soc. B. 97: 167, 1925.)

Man can continue to increase the intensity of work which demands more energy than can be supplied by his maximal oxygen intake during the work. This is done by increasing the recovery period. This phase of oxygen utilization becomes greater as the intensity of effort is increased. Hill has termed the amount of oxygen used during the recovery period the *oxygen debt,* for it indicates to what degree the body has gone into debt during the exercise,

TABLE XCIII

OXYGEN REQUIREMENTS FOR RUNNING 120 YARDS AT DIFFERENT SPEEDS (SARGENT[605])

SPEED (YARDS PER SECOND)	OXYGEN REQUIREMENT	
	LITERS PER 120 YARDS	LITERS PER MINUTE
5.56	1.83	5.08
6.45	2.71	8.75
7.15	2.94	10.50
7.24	3.08	11.13
7.70	3.85	14.81
8.40	4.33	18.17
9.10	6.27	28.46
9.23	7.36	33.96

a deficiency which must be made up after the exercise is over. Sargent[605] has shown experimentally that the oxygen debt may be as high as 16.3 liters. Values for the oxygen requirements for running at various speeds are given in Table XCIII.

Lactate Production.—The ability of man to go into oxygen debt is dependent, in part, on lactate production. Large amounts of lactate are found in the blood and urine of man immediately after strenuous muscular exercise. Hill and his associates[576] have recorded amounts as high as 204 mg. per cent (normal, 10 mg. per cent) and Liljestrand and Wilson[589] have found 1,370 mg. in the urine after exercise. Hill considered that the extra oxygen taken in during the recovery period was used only for oxidation of lactate produced during the exercise. However, this question has been reinvestigated by

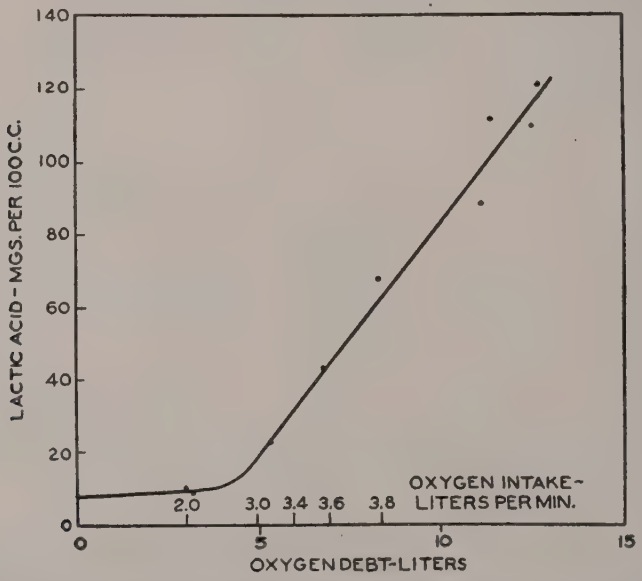


Fig. 307.—Relationship between lactic acid concentration in the blood and oxygen debt. Duration of exercise was ten minutes in each case. (From Margaria, Edwards and Dill: Am. J. Physiol. **106**: 689, 1933.)

Margaria, Edwards and Dill.[592] They found that a certain amount of oxygen debt may be increased without the appearance of lactate in the blood. When the oxygen debt reaches three or more liters, however, there is a direct relationship between the amount of lactate in the blood and the magnitude of the oxygen debt (Fig. 307). Therefore, the recovery period is made up of two phases, an alactacid debt which may be related to the oxidation of the usual food materials metabolized for the production of energy, and the lactacid debt which may be correlated directly with the oxidation of lactate.

Any experiments, however, of this nature in which blood concentrations are related to total energy exchange involve the assumption that there is an equal distribution of the material under study between tissues and blood. Sacks and Sacks[603] have stated that such conditions do not exist in cat's muscle, because the muscle lactate may be as high as 324

mg. per cent when the venous blood lactate is only 59 mg. per cent. These experiments indicate that measurement of blood lactate would not give any idea of the total amount of lactate in the body and any correlation between blood concentrations and oxygen consumption would be devoid of meaning. Newman,[596] however, has shown that in the rat there is a strict relationship between blood and tissue lactate concentrations.

These divergent results suggest that there may be a species difference. Therefore, the exact interpretation of the relationship of lactate concentrations in the blood and oxygen utilization by man during the recovery period must await a more complete analysis.

Sacks, Sacks and Shaw[602] have shown that for moderate degrees of muscular contraction there is always some lactate formed at the beginning of the period of contraction, but that this value soon falls off if the speed of contraction is not too great. This can only mean that the first phase of muscular contraction is anaerobic, since the respiratory and circulatory adjustments do not meet the need for several seconds after exercise has started. The work of Millikan[595] also illustrates this point. The muscle hemoglobin becomes reduced even when the blood supply is intact, thus proving that the demand for oxygen is greater than the supply.

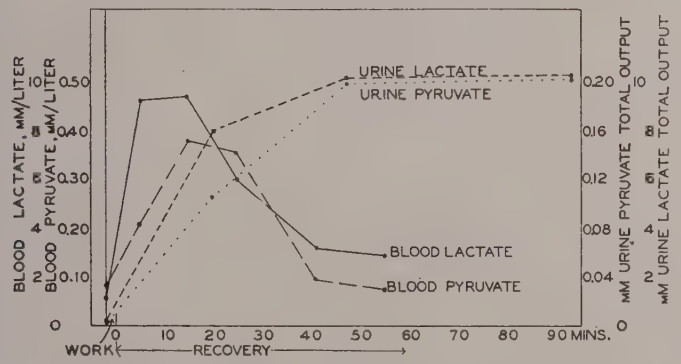


Fig. 308.—Relationship between lactate and pyruvate in blood and urine after hard running. (From Johnson and Edwards: J. Biol. Chem. 118: 427, 1937.)

The ability of the body to withstand the production of lactate is another limiting factor in muscular exercise. Recovery periods of 15 liters of oxygen have been reported. This indicates that a man can exercise to the degree at which he needs 20 liters per minute, five liters being taken in during the exercise and 15 liters afterwards. If he exercises for ten minutes, he must reduce the severity of the exercise, for he would have available only 6.5 liters per minute for his work: $\frac{10}{(5 \times 10 + 15)} = 6.5$. The relationship between the duration and velocity of work can be explained on this basis. For short distances, the runner may depend mainly on his recovery period; for long distances, he must run in a steady state and the metabolic cycles must be completed during the exercise. For moderate distances, the runner may depend on both factors. These facts are illustrated in Fig. 303. In this diagram the curve relating speed and duration is horizontal for short runs, falls off for moderate distances and again flattens out for long distances.

Pyruvate.—Pyruvate also appears in the blood and urine. The concentrations of pyruvate are very small in relation to the amounts of lactate. Johnson and Edwards[580] found that the ratio of lactate to pyruvate was thirty-seven five minutes after a strenuous run. Their results are given in Fig. 308.

EFFICIENCY OF MUSCULAR WORK

One of the important relationships obtained by the study of the total metabolism during and after work is the "efficiency" of man. This factor may be determined by relating the total energy to the output of mechanical energy. In this relationship the base line used is zero. Other base lines have been prepared: the basal metabolism, the metabolism of the subject sitting on the bicycle ergometer, and the metabolism of the subject pedalling without any resistance in the brake system. These values are subtracted from the total

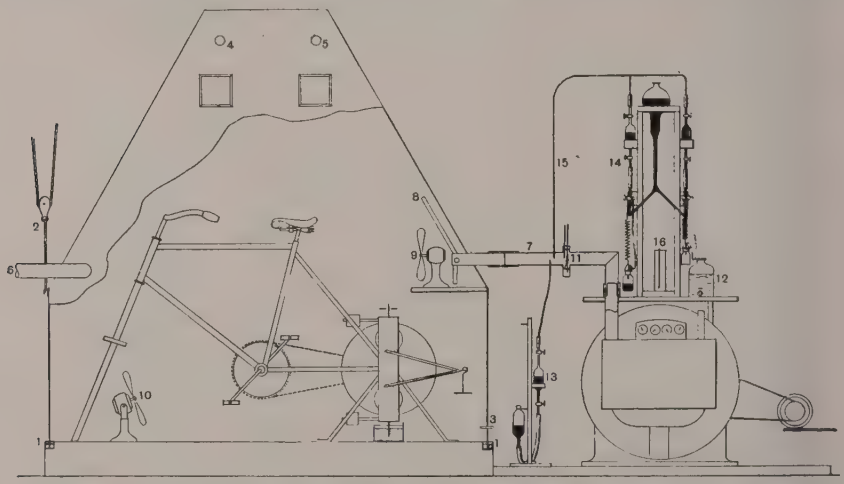


Fig. 309.—Bicycle ergometer, meter, and gas sampler. (From Krogh and Lindhard: Biochem. J. 14: 290, 1920.)

energy and are used in the calculation of a "net efficiency." Such a calculation indicates that the metabolism of work is an increment over a constant basal level. It is doubtful whether such a base line would remain constant during exercise. For example, some of the metabolic activity during rest is used to maintain body temperature. During work, there is a great excess of heat produced and it is dubious whether the body would continue to produce the basal amount of heat under such circumstances. Therefore, the best factor to use is the total output of energy in which the base line used is zero. However, if any other base line is used, the efficiency must be qualified by indicating what base line is involved in the calculations. Of numerous methods of measuring the mechanical energy developed by man during exercise, the most common is the bicycle ergograph (Fig. 309). The efficiencies of horses, men, and motors are given in Table XCIV. It is clear that another limiting factor in

the ability of man to carry out work is his power of converting only about 25 per cent of his total energy intake into useful external work.

TABLE XCIV

MAXIMAL EFFICIENCY OF HORSES, MEN AND MOTORS (BRODY AND TROWBRIDGE[544])

MOTIVE POWER	EFFICIENCY PER CENT
Steam Engines	15
Gasoline Engines	18
Horse	24
Man (stair climbing)	25
Diesel Engine	35

The maximal efficiency obtained in any process depends on the speed at which this process is carried out. This relationship has been determined for numerous types of work. The results of one such set of experiments are given in Table XCV in which the efficiency of man while pedalling a bicycle was determined. This relationship between speed of muscular movement and efficiency has important industrial application, since the highest efficiency of man may be obtained only over a very narrow range of speed of working. Not only does the speed of working affect the efficiency, but also the amount of work. Garry and Wishart[561] found that, with a light load on the bicycle, the efficiency was 13.9 per cent at 45 revolutions per minute. Increasing the load but keeping the speed constant, raised the efficiency to 16.0 per cent.

TABLE XCV

GROSS EFFICIENCIES OF MAN PEDALLING A BICYCLE AT VARIOUS SPEEDS WITH THE SAME LOAD (BENEDICT AND CATHCART[542])

REVOLUTIONS PER MINUTE	GROSS EFFICIENCIES (IN PER CENT)
70	20.6
80	20.0
90	19.2
100	18.4
110	17.6
120	16.9
130	16.1

The Respiratory Quotient During Work.—With the rise in oxygen consumption there is a corresponding increase in the carbon dioxide output. The change in the relation between these two variables, the respiratory quotient, has been studied extensively during muscular work. At the present time it is thought that moderate exercise does not change this quotient from the basal level. In the case of strenuous exercise, however, there is considerable disagreement among the investigators of this subject. The difficulty of obtaining an exact measurement of the respiratory quotient during severe exercise is due to the changes in the lactate content of the blood. Since this is a fixed acid its production results in the expulsion of carbon dioxide from the blood. Later, when the lactate is oxidized, there is a retention of carbon dioxide. Therefore, to determine the metabolic respiratory quotient, it is necessary to make collections of expired air *throughout the complete recovery period.* Hill and his associates (see Furusawa[560]) used the "excess respiratory quotient" as a measure of the metabolism during work. The quotient was obtained by subtracting from the total oxygen inspired and

total carbon dioxide expired during and after exercise the oxygen and carbon dioxide that the subject would have used and expired had he remained at rest during the same period of time. This calculation implies that the ratio of the carbon dioxide production and the oxygen consumption over and above the basal level will give a true combustion quotient for the period of work. The values obtained for this excess quotient averaged 1.01, and indicated to these authors that carbohydrate is the source of energy for muscular exercise in man. The difficulty in accepting the "excess respiratory quotient" as a basis for calculation lies in the fact that there is no evidence that the energy exchange of the "basal" metabolism remains the same in work or that the excess metabolism of work is exactly related to the increment over the basal level. Therefore the total respiratory quotient of exercise seems a better criterion of metabolism than the "excess quotient." Gemmill[563] determined the total respiratory quotients of men after they had run seventy yards in ten seconds on a treadmill. In these subjects the respiratory quotient including that of a complete recovery period was practically the same as the basal values. Dill and his associates[555] found that after severe muscular work the arterial carbon dioxide content did not return to the normal level during a two-hour recovery period. When the respiratory quotients were corrected for this shift in carbon dioxide tension, the "excess quotients" for the entire period of work and recovery were between 0.9 and 1.0. Christensen and Hansen[550] have found quotients of 0.95 with their subjects working at such a rate that 4.15 liters of oxygen were used per minute. These experiments show that some men working under very strenuous conditions have respiratory quotients less than unity for the metabolism during and after work.

THE FUEL OF MUSCULAR EXERCISE

Discussion of the respiratory quotient raises the question of the type of material oxidized by man in order to provide the energy for the muscular exertion. Liebig[587] observed a small increase in nitrogen in the urine after muscular work and from this observation concluded that protein catabolism supplies the energy for muscular contraction. Fick and Wislicenus,[559] however, calculated that the total amount of energy liberated during work is much more than that coming from the oxidation of protein. This conclusion has been confirmed by Cathcart[547] (Table XCVI). Although the metabolism of protein may be

Table XCVI

Effect of Muscular Work on Protein Metabolism (Cathcart[547])

	TOTAL NITROGEN OUTPUT IN GRAMS			
	EXPERIMENTS			
	I	II	III	IV
Pre-work (average, 4 days)	8.78	17.31	17.40	14.30
Work (average, 6 days)	10.01	19.96	18.23	15.44
Post-work (average 4 days)	9.05	17.76	17.34	16.34

responsible for a very small portion of the total metabolic change during exercise, other nitrogenous compounds, such as phosphocreatine and adenylpyrophosphate, have been shown to be of importance in muscular contraction. The

relationship of these substances to muscular work in the isolated muscle has been described in the chapter on the chemistry of muscular contraction (Chapter LII).

The question now arises as to the relative importance of the metabolism of fat and carbohydrate in supplying the energy. Benedict and Cathcart,[542] on the basis of their extensive study of the metabolism during muscular work, concluded that the more severe the muscular effort the more carbohydrate is oxidized but that exercise is not carried out exclusively at the expense of carbohydrate combustion. Krogh and Lindhard[584] also suggested that the energy for muscular work is obtained from the oxidation of both fat and carbohydrate. Recent work has substantiated the views of these observers. For example, Edwards, Margaria and Dill[557] observed that the respiratory quotient decreases with successive periods of work. From this observation they concluded that more fat is needed when the carbohydrate supply is diminished and that carbohydrate is no more essential for the metabolism of work than it is for energy exchange under basal conditions. Whether the fat must be transformed to carbohydrate before it is oxidized and whether fat may be utilized directly for muscular work are important questions that have not been satisfactorily answered at the present time.

TEMPERATURE REGULATION IN EXERCISE

Since only about 20 per cent of the energy expended during muscular exercise is converted into kinetic energy, the rest, about 80 per cent, is liberated in the form of heat. In order to lose this excess heat and to prevent an injurious rise in body temperature, various thermoregulatory mechanisms must go into action (see Chapter LIX). There is greater loss of heat through the respiratory tract associated with the increased ventilation of the lungs. Peripheral dilatation of skin vessels aids in loss by convection and radiation. The perspiration increases, allowing more water to be evaporated from the surface of the skin. Christensen, Krogh, and Lindhard[548] have drawn up a balance sheet for heat production and heat losses during exercise (Table XCVII).

Table XCVII

Balance of Heat Losses During Exercise (Christensen, Krogh, and Lindhard[548])
Work on ergometer for 180 min. at the rate of 1,080 kg. meters per min.

CALORIES PRODUCED		CALORIES EXPENDED	
Calculated from O_2 consumption	2,465	Mechanical work	472
		Rise in body tem.	107
		Lost by evaporation of water:	
		(a) through skin	956
		(b) through air passages	133
		Convection, radiation, and heating of inspired air	797
Total	2,465	Total	2,465

However, the thermoregulatory mechanisms cannot keep pace with the increased metabolic rate, for the body temperature rises somewhat during exer-

cise. Benedict and Cathcart[542] studied this rise during bicycle pedalling and obtained the results given in Fig. 310. It may be that the rise in temperature is an advantage to the body, as the velocity of metabolic processes would be increased and circulatory and respiration activity would be aided by this moderate change.

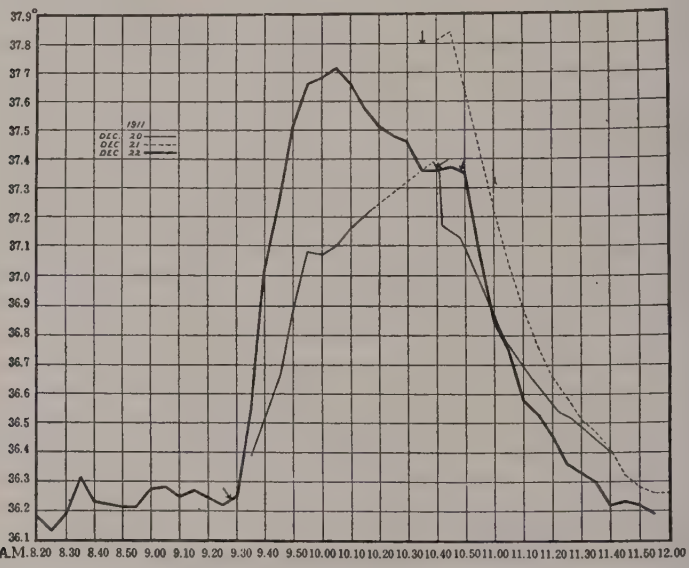


Fig. 310.—Continuous records of rectal temperature in a human subject during severe muscular work. (From Benedict and Cathcart: Carnegie Inst. of Washington, Publ. No. 187, 1913.)

BLOOD CHANGES

It is difficult in man to make direct analyses of the chemical changes in the muscles during exercise. Therefore, chemical studies must be confined to the blood and urine with the hope that the findings reflect the actual changes in the muscle. The difficulty of interpreting the results of blood analyses is that they represent only the transport of material to and from the active muscles. Nevertheless, some information concerning metabolic changes has been gained from these studies.

Numerous experiments have been made on the blood sugar content during exercise. Moderate work does not change the level of blood sugar, but if exhaustive work is carried out, the blood sugar may increase 10 to 66 per cent (Dill, Edwards and Mead[554]). If the exercise is continued for a long time, as in running a marathon race, the blood sugar may fall to very low levels (Levine, Gordon and Derick[586]). Numerous speculations have been offered to explain these results. It may be that during moderate work increased glycogenolysis in the liver keeps pace with the utilization of glycogen in the muscles and thus the glucose content of the blood remains constant. During more severe work

secretion of adrenalin may cause a more rapid liberation of glucose by the liver than is required by the muscles and, therefore, the blood sugar rises. However, if the exercise is extended over a long period of time, the supply of carbohydrate in the liver is exhausted and the blood sugar falls.

The lactate changes in the blood were discussed in connection with the oxygen debt. Laug[585] has correlated the changes in lactate, pH and the total CO_2 in venous blood during recovery from running 440 yards. Table XCVIII gives the results of a typical experiment.

TABLE XCVIII

CHANGES IN VENOUS BLOOD AFTER SEVERE EXERCISE (LAUG[585])

	PH	LACTATE (MG. PER CENT)	TOTAL CO_2 (VOL. PER CENT)
Resting	7.35	5.6	61.1
4'24" after running 440 yards	6.95	163.5	33.9
10'45" in 67.5 sec.	7.04	150.4	27.3

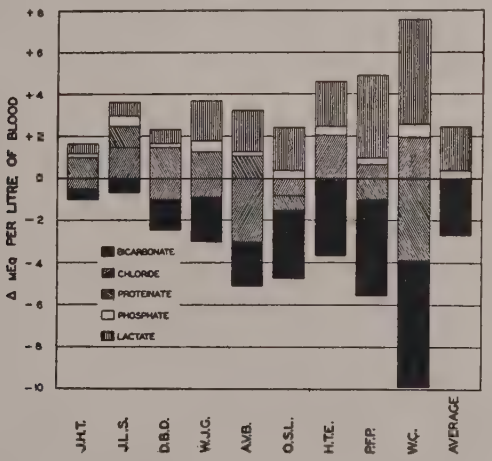


Fig. 311.—Changes in the principal anions of the blood serum during muscular work. (From Dill, Talbott and Edwards: J. Physfol. 69: 267, 1930.)

Gemmill[564] studied the changes in the acetone bodies after bicycle pedalling. No marked changes in these substances were found with the subjects on normal diets. However, on high fat diets there was a slight increase in these constituents following work. Changes in other blood constituents are summarized in Fig. 311. It is interesting to note that the concentration of the plasma proteins increases during exercise. These results may be accounted for by assuming a transfer of fluid from the blood to the tissues. However, the changes must be interpreted in the light of the severity of the exercise. There can be no doubt that in very severe exercise, with production of lactate in the muscles, there is a change in the water balance between blood plasma and tissues. During moderate work, in which lactate is not produced, there would not be the

necessity for this shift. Therefore, changes which are found during severe exercise cannot be transferred to all types of exercise.

There is an increase in the concentration of the red blood cells during work; the extent of the rise depends on the severity of the exercise (Table XCIX).

TABLE XCIX

THE EFFECT OF EXERCISE FOR FIVE MINUTES ON THE RED BLOOD CELL CONCENTRATION AND THE HEMOGLOBIN PERCENTAGE (SCHNEIDER AND CRAMPTON[606])

LOAD (FOOT POUNDS)	RED BLOOD CELLS (MILLIONS PER C.MM.)		HEMOGLOBIN (PER CENT)	
	REST	EXERCISE	REST	EXERCISE
4000	5.17	5.15	116	117
6000	5.16	5.43	115	120
8000	4.98	5.50	113	124
10000	5.16	5.80	114	127

Two theories have been proposed to account for these changes: (1) the red blood cells are forced into the circulation from reservoirs and (2) there is a change in concentration of the blood due to sweating, or passage of fluid from the blood into the tissues. Probably both factors, especially the latter, play a role in producing this change.

URINARY CHANGES

Wilson, Long, Thompson and Thurlow,[608] in a thorough study of the urinary changes following exercise, found that there is a decrease in urine volume and chloride concentration and an increase in hydrogen ions, total acid, ammonia and phosphate (Fig. 312). The drop in urine volume is due to a suspension of activity by the kidneys during exercise. It has been generally thought that this is due to a constriction of the renal vessels produced by the vasoconstrictor control. However, Verney and his associates[579] have obtained the same effect with the kidneys denervated. They postulate that the change in urine flow is due to the liberation of a hormone from the posterior pituitary during exercise. Further experimental work is needed before the exact mechanism of the decrease in urine formation can be explained. Factors which may operate are the change of water concentration in the blood and the increased loss of water through the skin and lungs.

The rise in acidity of the urine is explained by the increased acid excretion. Liljestrand and Wilson[589] have shown that as much as 1,370 mg. of lactate may be found in the urine after short periods of severe exercise. With this excretion of acid there is an increase in the ammonia output in an effort to save base. The mechanisms in the kidney for the production of ammonia cannot protect the body completely from the loss of base and some of these ions are lost. There is a slight increase in the phosphate excretion and the ratio of the disodium to the monosodium phosphate varies with the change in hydrogen ion concentration of the urine. Since this change is in favor of the monosodium phosphate, it also saves base. The small rise in phosphate excretion is probably a reflection of the changes in blood phosphate (Havard and Reay[571]). Since the mechanisms involving phosphate have been shown to be reversible in the isolated muscle, it is not surprising that the phosphate content of the

blood and urine does not change very much during and following exercise. In fact, Gemmill and Riberio[565] were unable to find that any change occurs in the blood phosphate of men as a result of running at maximum speed for ten seconds. The fall in chloride concentration may be due to the loss of chloride in the sweat and the shift of chloride with water from the blood into the active muscles. As in the case of blood changes, these urine changes found after severe exercise of short duration may not occur when man is exercising at a moderate rate of speed. They do illustrate, however, how the body is able to adjust itself to strenuous exercise. Moderate exercise may not call forth all these readjustments.

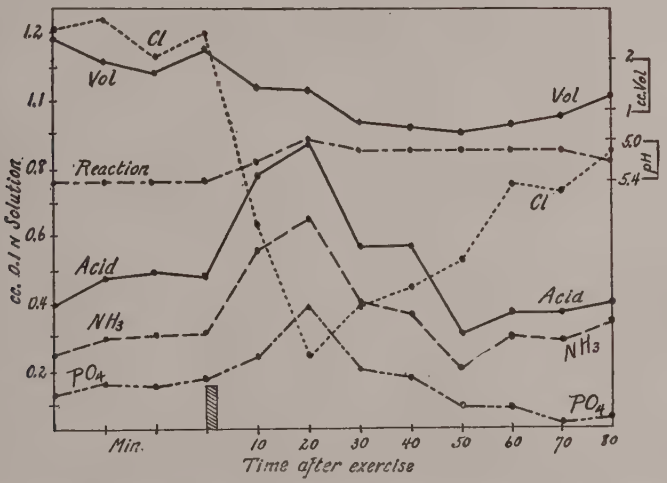


Fig. 312.—Chemical changes in the urine during and following severe exercise. (From Wilson, Long, Thompson and Thurlow: J. Biol. Chem. 65: 755, 1925.)

RESPIRATORY CHANGES

The total ventilation of the lungs increases with the demand for oxygen. The regulation is so exact that the value for the total ventilation is directly proportional to the utilization of oxygen (Fig. 313). For a given amount of work, there are two phases of the respiratory changes, a rapid initial increase followed by a slow rise to the final value which is maintained throughout the exercise. Since the onset of the initial phase is very rapid, occurring before any metabolites could affect the respiratory center, Krogh and Lindhard[583] have claimed that it is dependent on the higher centers sending impulses to the respiratory center at the same time that motor impulses are sent to the muscles. The final value reached depends on the severity of the exercise. The usual explanation of the change in ventilation during exercise is that the increased production of carbon dioxide raises the carbon dioxide tension of the blood which in turn excites the respiratory center. This, however, is not the whole story since in more severe types of exercise, with a continued increase in ventilation, the alveolar carbon dioxide tension may fall (Fig. 313). It may

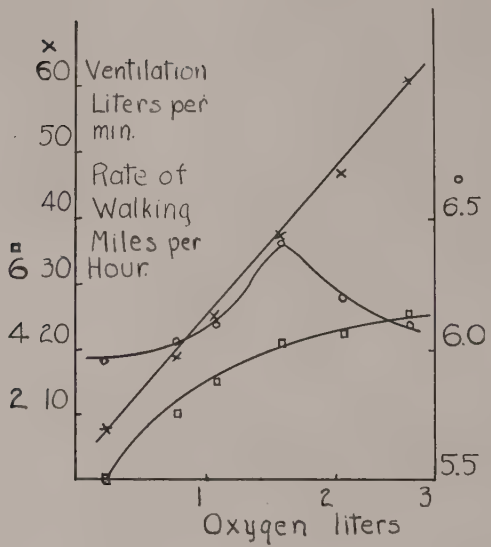


Fig. 313.—Relationship between oxygen consumption, total ventilation, and alveolar carbon dioxide during muscular work. Abscissa: oxygen consumption in liters per minute. Ordinates: *x*, total ventilation in liters per minute; *o*, alveolar carbon dioxide in per cent; □, rate of walking in miles per hour. (Drawn from data on page 29, Haldane: *Respiration*, Yale University Press, 1928.)

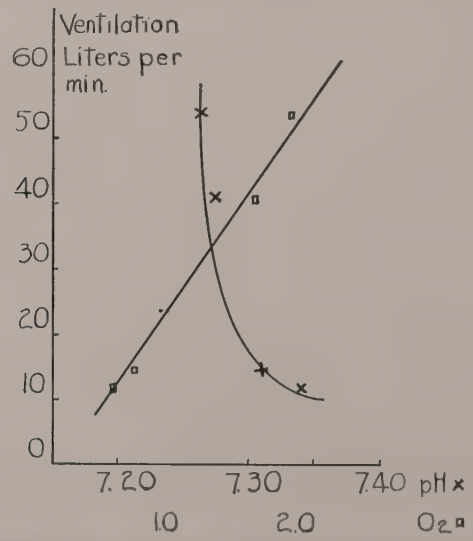


Fig. 314.—Relationship between pH, oxygen consumption, and total ventilation during muscular work. Abscissae: *x*, pH; □, oxygen consumption in liters per minute. Ordinate: total ventilation in liters per minute. (Drawn from Table 6, Arborelius and Liljestrand: Skandinav. Arch. f. Physiol. **44**: 215, 1923.)

then be assumed that at this point lactate is being produced and that the combined effect of lactate and carbon dioxide augments the respiratory effect. For more strenuous types of exercise, however, the proportionality between pH and total ventilation varies (Fig. 314). It appears that the respiratory center changes its sensitivity to chemical changes in the blood. More experimental work is needed before this remarkable agreement between total ventilation and the utilization of oxygen is explained satisfactorily (see page 604).

The maximal ability of the respiratory mechanisms to augment their activity to meet the demands of the body for obtaining oxygen and for ridding itself of carbon dioxide is another limiting factor in muscular work. The maximal limit for an average individual is about 80 liters of air per minute, although values as high as 113 liters have been reported (Robinson, Edwards, and Dill[601]).

CIRCULATORY CHANGES

With the augmented demand for oxygen by the active muscles, there is an increase in the amount of blood passing through these muscles. This increase in blood flow is produced by two things, an increase in cardiac output and a vasodilation of the capillary bed in the active muscles.

Cardiac Output.—Lindhard[588] has shown that during work the cardiac output varies with the metabolic rate. This is true when the same muscle groups carry out different intensities of work but does not hold when different groups of muscles are used. For example, Grollman[567] found that flexing the right thigh once per second raised the metabolism from 256 to 430 ml. of oxygen per minute and the cardiac output from 4.2 to 7.7 liters per minute, while flexing and extending the right forearm raised it to nearly the same value (453 ml.), although the cardiac output only reached 6.0 liters per minute. The differences are due to variations in the return of venous blood to the heart when different sets of muscles are used.

The increase in cardiac output during exercise is produced by (1) a more rapid heart rate and (2) a greater output per beat. Experimental data for these factors are given in Table C. The ability of the heart to pump blood

Table C

Relationship Between Cardiac Output, Heart Volume, Pulse Rate and Oxygen Consumption During and After Work (Liljestrand, Lysholm and Nylin[590])

CONDITION OF SUBJECT	AMOUNT OF WORK KG. METER PER MIN.	O_2 USED PER MIN. ML.	CARDIAC OUTPUT L. PER MIN.	PULSE RATE PER MIN.	OUTPUT PER BEAT ML.	HEART VOLUME ML.
Resting	----	312	3.2	56	57	670
Working	720	1557	9.7	131	78	650
Working	1260	2313	15.5	186	83	650
Recovery	----	398	4.8	80	62	635

is another important limiting factor in exercise. The maximal amount has not been determined because of the limitations of the methods for measuring cardiac output. Bazett (see page 403) has calculated, however, that in athletes a cardiac output as great as 27.5 liters per minute occurs during strenuous exercise.

Pulse Rate During Exercise.—It is a common experience that the heart beats more rapidly during muscular exercise. This phenomenon has been studied extensively by physiologists. A striking result of their study was the recognition of the rapidity of the increase; in fact, a shortening of diastole occurs during the first cardiac cycle following the commencement of muscular exertion (Buchanan;[546] Bowen[543]). Following the rapid initial increase, the

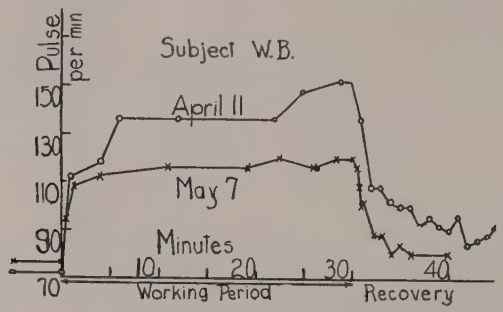


Fig. 315.—Pulse rates during work (bicycle riding) and recovery before and after training. (From Gemmill, Booth and Pocock: Am. J. Physiol. 92: 253, 1930.)

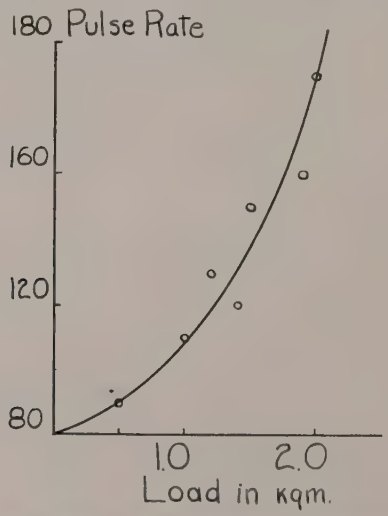


Fig. 316.—Relationship between pulse rate and load during muscular work in man. Abscissa: load in kilograms. Ordinate: pulse rate per minute. (Redrawn from Gillespie, Gilson and Murray: Heart 12: 1, 1926.)

heart rate gradually reaches a plateau. A typical curve showing these changes is given in Fig. 315. There are marked individual variations in the height of the rise. For example, Henderson, Haggart and Dolley[573] found that the pulse rates of athletes doing the same amount of muscular work varied from 126 to 152. In any one individual, however, there is a rough correlation between

pulse rate and the amount of work done[565] (Fig. 316). These authors also found that for the heavier loads the initial rise was much faster than for the lighter.

The return of the pulse rate to normal after exercise also occurs in two phases; a rapid drop is followed by a slow fall. Cotton and Dill[551] have observed that in the interval from ten to twenty seconds after exercise the pulse decreased at the rate of eleven beats per minute. Following this rapid drop, there is a slow return to the resting level. In fact, the postwork heart rate may remain above the prework level for one-half hour or more. Lythgoe and Pereira[591] have shown that the return of the heart rate to normal is slower than the recovery of the oxygen consumption.

Many physiological variables are involved in the explanation of these changes. Most authors agree that the primary rise is due to a reduction of vagal tone (Gasser and Meek;[562] Samaan[604]). Part of the secondary rise is due to the accelerator fibers of the sympathetic system. Complete removal of this system in dogs lessens the rise in rate by 30 to 40 per cent (Brouha, Cannon, and Dill[545]). It is interesting to note that the capacity for work of the sympathectomized dogs is not diminished. Another factor which must be considered is the presence of cardio-accelerator fibers in the vagal nerves. These fibers have been described by Jourdan and Nowak[581] as arising in the medulla and running down the vagi. Their endings are not affected by atropine and, of course, are not removed by sympathectomy. Their presence would explain the rise in pulse rate in the dog during exercise following removal of the sympathetic system and the injection of atropine. Brouha, Cannon, and Dill[545] concluded also that the cardiac acceleration was not due to the rise in body temperature, to muscular metabolites, to adrenalin, or to sympathin. Therefore, the factors which produce a rise in pulse rate during exercise are (1) a reduction of the tonic discharge of the cardio-inhibitor fibers of the vagi, (2) an increase in tonicity of the cardio-accelerator fibers in these nerves and (3) an increase in tonicity of the sympathetic accelerator fibers. Whether the same mechanisms work in all animals is not known; the conclusions given above apply only to the dog.

After exercise has started, the increased pumping action of the muscles and diaphragm increases the venous return. Hooker[578] found a definite rise in venous pressure in man during exercise. The increased venous return may evoke an acceleration of the heart rate, for in the anesthetized dog Bainbridge[538] found that the pulse rate increases reflexly following the injection of fluid into the veins (see page 469). The increased pressure at the junction of the great veins with the right auricle stimulates endings of afferent vagal fibers. The sensory impulses thus set up inhibit the tonic activity of the vagal cardio-inhibitory mechanism and, reciprocally, augment that of the sympathetic accelerator mechanism.

Systolic Output.—Not only does the rate of the heart increase, but also the amount of blood ejected at each contraction. Lindhard[588] reported changes of pulse rate from 66 to 90 during work, with an increase in the output per beat from 59 ml. to 100 ml. The increased venous return may dilate the heart and the cardiac muscle may respond to this with a greater force of contraction (Starling's law of the heart). Actual measurements have shown, however, that an increase in diastolic size occurs in only a few individuals (Meek and Eyster[594]). In other individuals, the systolic size changes with a decrease in the diastolic dimensions.

In these cases the increased stroke cannot be produced by change in the length of the cardiac fiber, but must be associated with a change in tension of the heart muscle.

Blood Pressure.—Two factors, increased rate and increased stroke volume, tend to raise the arterial blood pressure. Paterson[598] devised an apparatus to obtain systolic and diastolic blood pressures during work. The changes in systolic pressure found were proportional to the severity of the work, while the diastolic pressure showed only a slight increase (Table CI). The other main fac-

Table CI

Effect of Work on Arterial Blood Pressure and Pulse Rate (Paterson[598])

	ARTERIAL PRESSURE		PULSE RATE
	SYSTOLIC	DIASTOLIC	
Resting	122	72	85
Pedalling Bicycle			
"No load"	134	82	105
630 kg. per min.	170	90	140
840 kg. per min.	182	98	150

tor affecting the blood pressure is the peripheral resistance. The vasodilatation which occurs in the active muscles will be described. In addition, it is thought that during exercise the splanchnic vessels constrict and so shunt more blood into the muscles. This idea is assumed from rather scant experimental evidence. The only direct observation on this subject has been made by Barcroft and Florey.[540] They followed in dogs the color changes in an exteriorized patch of colon and found that short bursts of running resulted in pallor. During longer periods of exercise, the color returned to the colon. In the same animals, the spleen contracted and remained in the contracted state during the exercise period. It is impossible to state whether or not the colonic mucosa and the spleen represent, so far as the present question is concerned, fair samples of the splanchnic area.

Essex, Herrick, Baldes, and Mann[558] have succeeded in measuring the blood pressure, the pulse rate and, in addition, the coronary and abdominal arterial blood flow in a normal dog during exercise—a remarkable achievement. They found that the coronary blood flow increases more than 300 per cent, but returns very quickly to the resting level after the exercise is stopped. The blood pressure and pulse rates show marked augmentation during work and rapid return to the normal during the recovery period. In a later paper Herrick, Grindlay, Baldes, and Mann[574] reported on the flow of blood in the abdominal arteries during work. They found that the blood flow in the common iliac artery is increased, but the flow in the superior mesenteric, renal, and splenic arteries is not changed. These experiments do not rule out the occurrence of vasoconstriction in the splanchnic area during exercise, for the increased peripheral resistance may be overcome by the general rise in blood pressure. The effect may be either no change in blood flow or an actual increase—the effect observed by these authors. Other factors which may influence the arterial blood pressure are the effect of the change in the pH of the blood on the vasomotor center and the effect of chemical and mechanical stimuli on the receptors of the aortic arch and the region of the carotid sinus (see Chapter XXXIII).

Blood Flow Through Active Muscles.—Muscles are richly supplied with capillaries for adequate blood flow during muscular work. The capillary distribution in muscle is illustrated in Fig. 317. Many experiments on the rate of blood flow through active muscles have been made with different types of apparatus. The earlier workers, using the Ludwig stromuhr (see page 432), described a decrease in blood flow through the muscle during tetanic contraction and an augmentation after the contraction was over. The later experiments of Verzar[607] supported this idea. This author used the direct method of measuring the blood flow by attaching a pipette to a vein and determining the time necessary for filling the pipette. Anrep,[535] using a hot wire aerotonometer, has substantiated the view of the earlier workers. In contrast are the work of Rein[600] and Millikan.[595] These observers using dissimilar techniques claim that blood flow is not hindered by muscular contraction; in fact, it may be augmented. The explanation of these two divergent viewpoints may be found in the experiments of Barcroft and Millen[539] who measured the temperature of the plantar flexors of the leg of man during rhythmic contraction of the leg muscles and during various degrees of static work. The leg

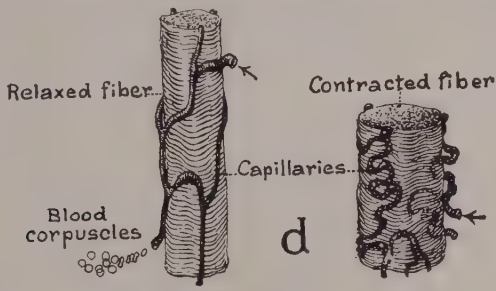


Fig. 317.—Relationship between muscle fiber and capillaries. (From Cullen and Brödel: Bull. Johns Hopkins Hosp. 61: 295, 1937.)

was subjected to external temperatures of 42° C. and 32.5° C., and at these temperatures the muscle temperature was 39.5° C. and 34.5° C., respectively. The assumption on which these experiments were done was that if the leg muscles cool on doing work at a high external temperature, or increase their internal temperature at the low external temperature, conclusion is that the flow of blood must be augmented. With this technique, these authors found that for rhythmic contraction and for low intensities of static work blood flow increased; for high degrees of static work, blood flow was impaired. These workers controlled their experiments by cutting off the circulation in order to get the magnitude of the temperature change that was due to muscular contraction itself. In the latter highly interesting experiments it was shown that with high intensities of muscular work, the amount and duration of work were not influenced by the absence of flowing blood. The discrepancies in the results obtained by the earlier workers are probably due to the differences in degree of the contraction employed by these observers. Therefore, we can accept the fact that light muscular work or rhythmic contraction increases the blood flow during the exercise and for some time afterward, but that heavy static work decreases or stops the blood flow during the exercise and only

increases it afterward. The fact that heavy static muscular work can be carried out without blood flow has also been demonstrated by Dolgin and Lehmann.[556] They determined the length of time that a man could hold a certain tension on a dynamometer with and without blood flow. For small tensions, the time decreased 59 per cent when blood flow was stopped; however, at higher tensions there was no difference in the duration, whether the blood flow was impeded or not. These results, with those of Bancroft and Millen, point directly to two types of metabolism in a muscle, the aerobic and anaerobic. Millikan's[595] experiments on the reduction of muscle hemoglobin show the same separation. Although during tetanic contraction the oxygen uptake is very rapid, the fact that the muscle hemoglobin is reduced with an intact blood flow demonstrates that the blood supply is unable to meet the oxidative demands of the muscle. Nevertheless, considerable tension may be developed and maintained under anaerobic conditions in man.

Vasomotor Control in Muscles During Contraction.—The increase in blood flow during and after work described in the previous section is due to three factors: dilatation of muscle capillaries, increase in arterial pressure, and the pumping action of the muscles themselves. Direct observations on the increase in the number of open capillaries in a muscle following contraction have been made by Krogh[582] and Ni[597] in frog's muscles. Ni found that in a resting muscle of a frog there were ten capillaries open per sq.mm. and that on stimulation the corresponding muscle on the other side showed 182 patent capillaries. Hartman and his associates[570] have studied the capillaries in the cat's sartorius muscle and have observed that faradic stimulation of the femoral nerve causes dilatation. In the gracilis muscle of the dog, Martin, Wooley and Miller[593] found 1,050 open capillaries per sq. mm. in the resting muscle, and 2,010 open capillaries in the exercised muscle. In a similar area there were 1,690 muscle fibers. Therefore, there is more than one open capillary per muscle fiber during exercise.

The opening of the capillaries may be due to neural and chemical influences. There are three ways in which vasodilatation in a muscle may be brought about by neural influences: by a decrease in vasoconstrictor tone or by an increase in vasodilator discharge, or by the concurrent operation of both of these factors. In normal animals, the decrease in vasoconstrictor tone is generally the most important factor, but activity of vasodilator fibers may play a role.

In sympathectomized cats, vasodilatation occurs when the animal struggles. This was interpreted by Pinkston, Partington and Rosenblueth[599] as being due to the discharge of impulses over dilator fibers in the dorsal spinal roots, but Bacq, Brouha and Heymans[537] state that the important factor under these conditions is the production of metabolites. The former authors claim a species difference, the change in blood pressure being not so marked in dogs, and the difference between cats and dogs being attributable to the more efficient vasodilator nerves of the cat. The role played by vasodilator fibers in the normal animal during muscular exercise has not been ascertained; and the exact pathways of the afferent stimuli to the vasomotor centers are not known. The importance of the carotid sinus mechanisms and the effect of direct stimulation of the vasomotor center by metabolites or by impulses from the higher centers are also in doubt. Nevertheless, there can be no doubt that neural mechanisms play an important part in the vasodilatation as they do in the increase in the heart rate during exercise.

Our knowledge of the mechanism of chemical control is not in any better experimental state than the neural. Gaskell, in 1877, showed that lactic acid

produces vasodilatation, and many others workers have demonstrated that a fall in pH produces the same effect. However, Ni[597] has shown that the capillaries dilate when iodoacetate is present in concentrations sufficient to block lactate production. Carbon dioxide also is a well-known vasodilator, and exerts the same effect as other acids which produce the same pH change. The amounts which have been used experimentally are far greater than those which are produced normally. Anrep[534] has stressed the production of a vasodilator substance, present in the venous blood, which has all the pharmacological properties of histamine. Adenylic acid has also been suggested as a possible chemical vasodilator. There can be no doubt that chemical substances, which may cause vasodilatation, may be produced during muscular contraction.

DIGESTIVE SYSTEM

Hellebrandt and Tapper[572] made a study of the influence of work on the secretory and motor functions of the stomach during exercise. They observed that the secretory response of the stomach to a test meal is inhibited and a fluoroscopic study of gastric motility revealed inhibition of gastric peristalsis. Since the motor inhibition was followed by increased activity the resultant of the two processes gave a normal emptying time of the stomach. Probably similar changes occur in intestinal motility and digestion.

CHAPTER LIX

THE REGULATION OF BODY TEMPERATURE

By Philip Bard

The classification of animals into two groups—warm-blooded (homoiothermic) and cold-blooded (poikilothermic)—according to their ability to maintain body temperature at a constant level, is more or less arbitrary. Between the two groups another exists, represented mainly by hibernating animals, in which at certain times of the year the animal is warm-blooded and at other times cold-blooded. The ability of the higher mammals to maintain a constant body temperature may or may not be present at the time of birth. The heat-regulating mechanism of the human infant, for example, remains ill developed for some time, so that exposure to cold is liable to lower the body temperature to a dangerous degree.

NORMAL VARIATIONS IN BODY TEMPERATURE

In animals in which the heat-regulating mechanism is fully developed, there is not, even during perfect health, entire constancy in temperature in the different parts of the body or in the same part at different periods of the day. The average rectal temperature of man is usually stated as being 37° C. (98.6° F.), but the normal diurnal variation may amount to 1° C. (1.8° F.), being highest (37.3° C., or 99.1° F.) in the late afternoon and lowest (36.3° C. or 97.3° F.) during the early morning hours. There are probably several causes for this variation, and they are in part at least dependent upon the greater metabolic activities of the waking hours and upon the taking of food. Apart from these influences, however, others which are less evident appear to operate; for it has been found that, when the daily program is reversed by night work, the usual diurnal variation, although much less pronounced, still remains evident even after this reversal in habit may have been kept up for years. It is of interest to note in this connection that nocturnal birds have their maximum temperature at night and their minimum during the day.

Regarding the temperature in different parts of the body, that of the rectum is usually about 1° C. higher than that of the mouth, which is again higher than that of the axilla. Of these three the mouth temperature is the most variable, for many conditions, such as mouth-breathing, talking, drinking cool liquids and even exposure to cold air, are sufficient to lower markedly the temperature of this region. Greater differences in the temperature of these different regions of the body are often observed in feeble individuals and in those with some circulatory disturbance.

It is not correct to state that the blood possesses an absolute thermal constancy. Venous blood from active muscles may be a degree or more above that from the skin, especially if the latter is losing heat rapidly. Doubtless the mixed venous blood of the venae cavae and right heart and the blood in the

central arteries exhibit a much greater constancy, but even here there may be some variations. The liver and other internal organs are normally several degrees warmer than the rectal cavity.

FACTORS WHICH MAINTAIN THE BODY TEMPERATURE RELATIVELY CONSTANT

The body temperature represents a balance between heat production and heat loss. The various factors which operate to achieve this balance are illustrated in a chart constructed by Du Bois (Fig. 318). At the bottom of this is represented a pair of scales one of which is weighted with heat production,

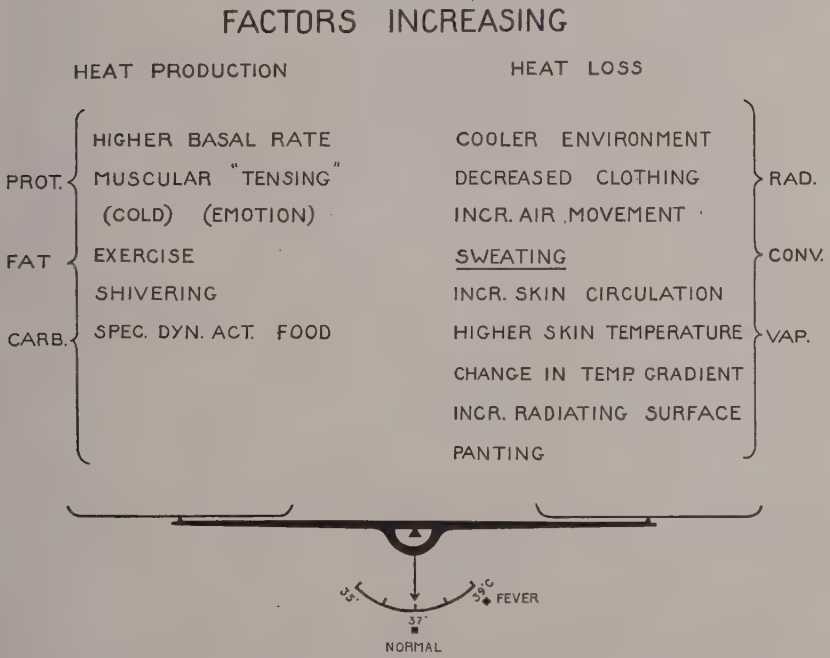


Fig. 318.—Diagram showing the more important factors which increase heat production on the one hand and heat loss on the other. Those which increase heat production do so through an increased metabolism of protein, fat, and carbohydrate in varying proportions. The factors which increase heat loss do so by increasing radiation, convection, and vaporization. The diagram of the balance indicates that heat production and heat loss are almost always in equilibrium, so that a normal body temperature is maintained at an average of 37° C. (From Du Bois: *Lane Medical Lectures: The Mechanism of Heat Loss and Temperature Regulation.* Stanford University Press, 1937.)

the other with heat loss. Normally the two pans are equally loaded and the pointer of the balance is at 37° C., which is the average normal temperature. As Du Bois[619] states: "Throughout the day there are slight changes in balance, as one factor or another predominates temporarily; but an adjustment made through the temperature-regulating center loads the opposite pan and brings the scale into equilibrium." This is the way in which all warm-blooded animals (birds and mammals) maintain a relatively constant temperature.

Changes in heat production which occur in the process of regulation constitute what is known as the *chemical* control, while alterations which modify the heat loss are spoken of as *physical* methods of control.

In his excellent account[627] of thermal adjustments in man and animals C. J. Martin points out that the mechanism of control is not like an ordinary thermostat which turns on and off the heat. A control of this sort could serve adequately only so long as the temperature of the body was well above that of its surroundings. Because of the fact that heat production cannot be reduced below a certain minimum, a simple thermostatic device would be unable to prevent a rise in body temperature when the environmental approached the body temperature. On the other hand, a regulating mechanism which functioned only by controlling the rate of heat loss would require a high consumption of fuel and would limit the range of environmental temperature compatible with a constant body temperature. As Martin puts it, the higher mammals and the birds have compromised and use both methods.

Regulation of Temperature by Altering Heat Production (Chemical Control).—This is effected by changes in the amount of combustion going on in the cells of the body. Heat production occurs mainly in the skeletal muscles where exothermic oxidative and nonoxidative reactions are constantly going on. When the activity of the muscles is abolished by curare, the temperature of the warm blooded animal immediately falls. Increased muscular activity, on the other hand, promptly raises the body temperature by 1° or 2° C. (Fig. 310). Normally a further rise does not occur, for the excess of heat is lost from the body through the operation of physical control. The temperature in such cases adjusts itself at a higher level where it remains fairly constant however strenuous the exercise. A certain amount of heat is also generated by the chemical processes occurring in the liver and other viscera, but when compared with the muscles this source is undoubtedly insignificant. The heart, of course, contributes some heat. It should be realized that all the mechanical energy liberated by the cardiac muscle is converted to heat within the body, for the energy of blood flow is spent in overcoming the frictional resistance of the blood vessels.

The production of heat goes on all the time in all tissues because of their resting energy requirements. In muscles the condition of tonic contraction present even at rest adds to this basal heat. When more heat is required by the body there may be an increase in tone, a "tensing" of the muscles, but this is not easily detected. Shivering, which is a special thermal response to a lowered environmental temperature, apparently consists of synchronous contractions in small groups of muscle fibers, repeated out of phase with those of other groups so that no extensive pull is exerted on the tendon. When more heat is required than can be obtained by this activity, the animal instinctively moves about in order that greater contractions may liberate more heat.

Heat is also set free by the specific dynamic action of the foodstuffs, and advantage may be taken of this to produce more heat when the cooling conditions are excessive; in winter, for example, there is an inclination to take more protein food, which has the highest specific dynamic action, than during summer. The per capita consumption of protein is said to be much greater in peoples living in temperate zones than in those living in the tropics.

It is well known that the metabolic rate is influenced by several glands of internal secretion. Of these the thyroid exerts the greatest direct influence on heat production. Complete thyroidectomy lowers the rate of combustion to a level about 40 per cent below normal, while the basal metabolism may be doubled in severe cases of hyperthyroidism. Thyroid activity is

apparently not subject to rapid changes, and there is thus little basis for supposing that the gland plays a part in the quick alterations in heat production which characterize most of the responses to environmental heat and cold. It may, however, be of some importance in certain slowly developing adaptations. For example, it is known that the thyroids of range cattle appear to be more active in winter than during the warm months of the year. The secretory activity of the thyroid is under the control of the anterior lobe of the pituitary which exerts its influence through the secretion into the blood of a thyrotropic hormone (see page 1030), but little is known of the circumstances which may modify the control. Recently, however, some light has been thrown on one aspect of this problem. Uotila[635] has obtained evidence that the increased secretion of thyrotropic hormone and the thyroid hypertrophy which normally occur in rats as a result of prolonged exposure to cold is prevented by previous section of the pituitary stalk. It is established that nerve fibers pass from the hypothalamus to the pituitary by way of the hypophysial stalk (see Chapter XVII) and these results suggest that normally long exposure to cold causes the production of increased amounts of thyrotropic hormone by provoking a discharge of nerve impulses over fibers belonging to the hypothalamico-hypophysial system (see page 192). It appears that the normal output of thyrotropic hormone is not dependent on the pituitary stalk; evidently it is determined by humoral rather than nervous influences. If there is a nervous control of the thyroid—the evidence on this point is slight and somewhat conflicting—it must be of minor significance in the regulation of body temperature.

The one endocrine organ whose activity is known to be subject to rapid changes induced through its nerve supply is the adrenal medulla. Furthermore, it is known that adrenalin has a calorigenic action in the body. These facts suggest that this gland may play a part in the processes of temperature control. As we shall see, there is evidence that it does, but consideration of this aspect of the subject will be postponed until we have reviewed the subject of physical control.

Regulation of Temperature by Altering Heat Loss (Physical Control).—Loss of heat from any body, animate or inanimate, can occur through conduction, radiation, convection, and vaporization. The amount of heat lost through these four channels depends chiefly on the surface area of the body and the difference between its temperature and that of the surroundings. For an understanding of the roles played by these methods of heat loss in the regulation of body temperature it is necessary to bear in mind certain facts of elementary physics.

Conduction.—This is a process in which heat is transferred through a solid, liquid, or gas from one molecule to another at a rate which depends on the thermal conductivity of the substance and the difference in temperature between the two points under consideration. The *heat conductivity* of a substance is the quantity of heat, measured in calories, transmitted per second from one face to the opposite face of a centimeter cube of the substance when the difference in temperature between the two faces is 1° C. The conductivities of certain substances are shown in Table CII. It is evident that many common materials and substances differ greatly in their capacities to transmit heat by conduction. Silver, as everyone who has stirred a hot liquid with a spoon made of this metal knows, is an excellent conductor. The great difference between brass and wood in this respect may easily be appreciated by placing one's hand momentarily first against a wooden door and then on the brass door handle or knocker. In doing this one may gain an erroneous conception of the temperatures of the two materials; although they are actually at the same tempera-

ture, the brass feels much cooler than the wood for the reason that being a much better conductor it abstracts heat very much more rapidly and so cools the skin very much more quickly. It should be noted that water is a relatively poor conductor. The fact that air stands near the bottom of the list is important physiologically. Thick hair, feathers, and clothes (especially woolen garments) serve to reduce loss of heat from the body not only because they are themselves poor conductors but also because they contain air in their meshes. A glance at Table CII explains why eiderdown, which is light and elastic, has been preferred by the luxurious as a material for beds and coverlets.

TABLE CII

HEAT CONDUCTIVITIES (COEFFICIENTS OF CONDUCTIVITY) OF VARIOUS SUBSTANCES (COMPILED FROM VARIOUS SOURCES)

SUBSTANCE	TEMPERATURE ° C.	CONDUCTIVITY
Pure silver	18	1.006
Brass	ordinary	0.225
Sandstone	ordinary	0.0055
Glass, soda	20	0.0017
Water	17	0.00131
Leather (cowhide)	ordinary	0.0004
Dry soil	ordinary	0.00033
Fir wood, along the grain	ordinary	0.00047
Fir wood, across the grain	ordinary	0.00026
Air	0	0.0000568
Wool	ordinary	0.000054
Eiderdown	ordinary	0.000011

Radiation.—It will be recalled that radiant heat is transmitted by electromagnetic waves which like light waves are subject to interference, reflection, refraction, and polarization. Heat waves and light waves are identical except as regards wave length, and they all travel at the same velocity (about 186,300 miles a second). Radiation is the means by which enormous quantities of energy are transferred every day from the sun to the earth across the perfect vacuum of space. When radiant energy falls upon a body, energy of wave motion is transformed into heat. If the body absorbs 100 per cent of the radiant energy that falls on its surface, it is called a *perfect black-body*. Air is a very poor absorber of heat and therefore the radiant energy of the sun passes through the earth's atmosphere with relatively little loss, strikes the ground and is transformed into heat which warms the air by conduction and convection. The same principles apply to the situation in a room warmed by a stove; radiant energy from the stove does not to any extent directly heat the air in the room; it heats the walls (especially the opposite wall), tables, chairs, persons and other objects in the room because they absorb these electromagnetic waves emitted by the stove and in turn lose by conduction and convection (and if moist also by vaporization) some of the heat thus gained. Similarly, a person, as a result of the heat liberated by metabolic processes, radiates energy through the air to other objects. Du Bois[619] has clearly corrected a common misconception by stating: "It is a mistake to think that we radiate to the surrounding air; we radiate through the air to the solid objects in the vicinity. A man sitting in a heated room in the winter time loses a good deal of heat toward a cold window pane, and less heat towards the walls and ceiling. He receives radiant heat from the steam radiator." Of course when a number of people are crowded together they radiate toward one another and in this process each gains as much heat as he loses. Also, parts of one individual radiate to each other, e.g., the inner surfaces of the thighs, and so block each other off as far as loss of heat from the body is concerned. For this reason the effective radiating surface of a man is about 80-85 per cent of his total surface area.

The amount of radiation from an object is determined by several factors. It is proportional to the surface area of the body, to its emissive power and to the difference in temperature between the radiating body and the body to which it is radiating (actually to the difference between the fourth power of the absolute temperature of the radiating body and the fourth power of the absolute temperature of the object to which it is radiating).

The electromagnetic waves by which heat energy is transferred are of different lengths and lie within the scale of radiation which extends from the very short cosmic rays (0.0005

ångström) at one end to the very long radio waves (beyond 2.2×10^6 Å) at the other. As it reaches the earth the sun's radiation extends from the short ultraviolet (about 2,800 Å) to the near infrared (about 30,000 Å). The rediation from a red hot stove starts in the visible red (at about 6,500 Å) and ends in the far infrared. That from the human skin is distributed through the near infrared; it begins at a wave length of about 50,000 Å, reaches a peak in intensity at 90,000 Å, and extends to 200,000 Å (see Hardy[620]). Now it has been determined that the human skin, white or black, is a 97 per cent perfect blackbody.[620] At first thought it may seem hard to understand why there is no essential difference in this respect between the skin of a dark negro and that of a white man, but the following quotation from Du Bois[619] should clarify the matter: "The explanation lies in the fact man does all his radiating at wave lengths beyond the visible, and there is certainly no difference in color between a white man and a black man in a dark room in the middle of a moonless night."

Convection.—This form of heat transfer is limited to fluids and gases. It is simply a mechanical process of mixing in which a cooler fluid or gas comes in contact with warmer fluid or gas, becomes heated by conduction and carries heat elsewhere. Convection is the process whereby heat is carried up a chimney; the heated air rises because its density is less than that of cold air. Similarly, when a flame is applied to a beaker of water, the water eventually becomes equally heated all through because of convection; but first the water just over the flame becomes hot by conduction through the glass, then the colder water above displaces the hot water because it is heavier and finally mixing leads to an equal heating of all the water. In both these examples the mixing is automatic. On the other hand, the forcing of a current of cool air over a heated body cools that body by convection; such is the principle of the radiator of an automobile. When a man sits in a draft, the air near his skin, air which has been warmed by conduction, is replaced by cold air which in turn is warmed, and thus heat may be continually abstracted from the surface of his body. This process must be clearly distinguished from loss of heat by vaporization of water from the body surface, a process which is of course facilitated by movement of air. Because the specific heat of water (1.00) is so much greater than that of air (0.1692-0.2374), loss of heat by convection must be very great in the case of a man swimming in cold water.

Vaporization.—This process of heat transfer depends on the fact that it requires a definite amount of heat to change a given amount of any liquid into vapor without changing the temperature. For example, when water is boiling at one atmosphere it takes 539 small calories to evaporate one gram without changing the temperature of the water. This quantity is called the heat of vaporization of water. The change in water from a liquid to a gas involves the loss of heat from surrounding materials (including the liquid itself) and they are thereby cooled. Conversely, if a given amount of water condenses on an object it gives to the surroundings the same amount of heat which it took from them on vaporizing. In the case of the human body each gram of water vaporized from the surface at room temperature entails the loss of about 580 small calories and this is the figure which has been used in calorimetry experiments. The total amount of vaporization of water from a body depends on its surface area, the temperature of the surface and on the vapor tension and movement of the air. Liquids undergo evaporation at all temperatures, but the region over the free surface of the liquid may contain so much vapor that condensation occurs as rapidly as vapor is formed; when this is the case, the atmosphere over the liquid is said to be saturated. It must be remembered that as air is warmed its capacity to hold moisture is increased. Therefore on a very hot and humid day evaporation of sweat may still be an effective means of preventing a rise in body temperature. The ratio of the actual moisture content of a given volume of air to the maximum content possible at the same temperature is the *relative humidity*. It has been determined that a relative humidity of 40 to 60 per cent is desirable for comfort and health. When a body is at a temperature below that of its surroundings it can lose heat only by vaporization; it will at the same time of course be gaining some heat by the other means of thermal transfer.

Heat loss in man is effected mainly through the skin, but partly through the respiratory tract and lungs. The amount of heat lost through the feces and urine is such a small fraction of the total loss that it can be disregarded in all but the most accurate determinations. Through the skin heat is lost for the most part by radiation, convection, and vaporization of water. Through

the respiratory tract and lungs it is lost mainly by vaporization, but partly by convection as the inspired air is warmed; an increased ventilation augments the loss through the respiratory tract chiefly by increasing the vaporization.

In the case of human beings conduction is rarely an important means of heat loss. It occurs chiefly when a portion of the bare skin comes in contact with a good conductor, as when a boy after swimming sits on a cool stone in the shade. If a man lies on the cold ground in thin clothes some heat may be lost in this way. We voluntarily reduce heat loss by wearing clothes which, as already pointed out, are poor conductors and which trap in their meshes air which is an equally poor conductor.

It is obvious from what has been related that the proportions of heat lost from the body by the processes of radiation, convection, and vaporization are determined by the temperatures of the skin and the surroundings, by the movement of air over the skin and respiratory surfaces, and by the amount of water vapor in the air. The temperature of the skin of course depends on the rate at which blood passes through the cutaneous vessels. A brisk circulation here is essential for any considerable loss of heat by any of the three means of heat transfer just mentioned. On the basis of data compiled by Rubner and Aldrich, Martin states that of the total heat dissipated by a man, clothed and sitting in a room at 15° C., with the air 50 per cent saturated, about 44 per cent is lost by radiation, 31 per cent by convection, and 20 per cent by evaporation from skin and lungs. By means of measurements which involved the direct and accurate determination of the heat lost by radiation from the body surface Du Bois and his colleagues[619] have obtained similar figures. Hardy and Du Bois[621] determined with great accuracy that, in the case of a naked man lying quietly in a calorimeter where the temperature is 27.4° C. (a neutral temperature as regards basal metabolic rate) and the humidity 25 per cent, the loss of heat is distributed as follows: 58 per cent by radiation, 27 per cent by vaporization of water, and 15 per cent by convection.

Different conditions change not only the total amounts of heat produced and lost but also the proportions lost through the three different channels. For example (see Du Bois,[619] page 71), under basal conditions a normal man who was losing slightly more than 100 calories per hour was getting rid of 66 per cent of this heat by radiation; 15 per cent by convection and 19 per cent by vaporization of water. Then, when this same individual engaged in three vigorous games of squash rackets his heat loss increased more than fivefold, but the absolute amount of heat lost by radiation increased only slightly and a large increase in rectal temperature was prevented chiefly through increases in the losses by convection and vaporization, particularly the latter. Thus, at the end of the second game 12 per cent was being lost by radiation, 13 per cent by convection and 75 per cent by vaporization. Although the total heat lost was approximately five times that lost at rest under basal conditions, the heat production had risen even more, and this fact was reflected in a rise in rectal temperature from 37.6° to 38.8° C. At the same time there was a fall of nearly 2° C. in skin temperature, the result of the cooling effect of an enormous vaporization of the water produced by sweating. There was, therefore, a great cooling of the blood flowing in dilated vessels immediately below the surface of the body, but even this did not suffice to balance the augmented production of heat. The absolute increase in loss by convection was due to movements of the body in the course of the exercise.

Convection becomes a more important means of heat loss when moving air passes over the body surface or the body moves through still air. It is easy to understand how loss by convection increases when one sits in a draft or moves rapidly through air. But convection sometimes plays a more subtle role in heat loss. In 1918 Barr and Du Bois reported that a patient may lose more heat during a malarial chill when the skin is cold than in the period before the chill when the skin is warm. Of course a cold skin loses less heat by radiation and evaporation than a warm skin and the explanation of this rather surprising finding did not come until recently when the development of the Hardy radiometer made it possible to measure very accurately the amount of heat lost from the human body by radiation and so to separate the loss by convection which cannot be determined directly, but must be calculated by subtracting radiation and vaporization from total heat loss. It appears that the movements (shivering) which occur during a malarial chill may so increase the loss of heat by convection that the total loss from the cold skin may be equal to or even greater than that from a quiet warm skin. The effect of shivering is beautifully illustrated in an experiment described by Du Bois.[619] A naked subject entered a calorimeter where the air temperature was 22.7° C. He felt cold and his skin temperature dropped steadily (from 31.8° to 29.9° C.) during an initial period of nearly two hours. Then he began to shiver violently and during twenty-one minutes of this involuntary exercise his skin temperature rose only 0.5°-0.75° C. Now during the shivering period radiation was less than before but total heat loss was greater because convection was greatly increased on account of the movements; loss by convection was 29 per cent of the total as compared to 15 per cent during the period before shivering began. Interesting as these facts are, it must not be forgotten that with body movement far greater quantities of heat are lost by convection from a warm skin than from a cold skin and that shivering as a means of maintaining body temperature in the face of cold is not seriously counterbalanced by increased loss of heat through convection.

The Role of the Circulation in Physical Regulation.—Under average environmental conditions the main regulation of body temperature is effected by variations in the skin temperature brought about by cutaneous vasoconstriction and vasodilatation. These two processes, by altering the amount of blood flowing through the skin, decrease and increase the amount of heat lost by radiation, convection, and vaporization. The cutaneous blood flow is regulated not only by changes in arterioles, capillaries and veins, but also by the state of the arteriovenous anastomoses[615] which occur in large numbers in the extremities and are provided with innervated contractile cells. It appears that a very effective flushing of certain portions of the skin with blood can be achieved by the opening of these anastomoses. When cutaneous vasodilatation or vasoconstriction occurs in response to changes in environmental temperature it appears that an opposite change takes place in vessels of the interior of the body (see page 473) in order to maintain the capacity of the vascular system within reasonable bounds.

The marked sensitivity of the cutaneous blood supply to changes in the temperature of the environment has been pointed out (page 444). When the blood flow through the hand is examined in a person who has been exposed to the outside air, it may be little more than half that which it attains after he has been in a warm room for some time. In the outside air the vessels constrict to prevent heat loss by convection and radiation; in the warm room they dilate to facilitate this loss. The afferent impulses which reflexly control the change in the cutaneous blood circulation may be set up by local applications of heat or cold, as can be shown in hand-calorimeter experiments by applying a cold pad to the skin of the corresponding forearm, or allowing an electric fan to blow on the arm when an immediate curtailment of blood flow takes place. Or the reflex may be excited from distant skin areas, as illustrated in the curtailment in blood flow observed when the hand opposite to that on which the

observation is being made is placed in cold water. The magnitude of the change in the cutaneous circulation is more or less dependent upon the extent of the area of the body that is exposed to the change in temperature.

Vasomotor responses to temperature changes are greatest in the extremities which, of all parts of the body, are the most effective dissipators of heat. Burton[611] has shown that the blood flow through the human fingers can change over the enormous range of from 0.5 or 1.0 ml. to 80 or 90 ml. per minute per 100 ml. of tissue. In the hand the range is smaller, from 1 ml. to about 20 ml. (Freeman), and it is doubtless narrower in more proximal parts. The tremendous range of flow found in the extremities cannot possibly reflect a range in metabolic requirements, for in the case of the fingers, which contain little muscle, Burton calculated that the minimum value corresponds to the flow necessary to meet the oxygen demands of the skin; the range must represent a mechanism for temperature regulation by elimination of heat.

The Role of Vaporization in Physical Regulation.—When the loss of heat by radiation and convection is no longer adequate to prevent a rise in body temperature, or when these processes cannot operate effectively on account of a high environmental temperature, the necessary loss of heat from the skin is dependent upon the *evaporation of sweat.* A naked man lying quietly and surrounded by air at 34.5° C. is covered with sweat and his entire heat loss is by vaporization.[619, 622] Under ordinary or basal conditions, however, a man secretes little or no sweat; yet he vaporizes about 30 grams of water per hour and thus loses about 17.4 (30 × 0.58) large Calories. When individuals born without sweat glands are studied in a calorimeter under basal conditions it is found that they vaporize the same amount of water as do normal individuals. This evaporation of water constitutes the greater part of the weight loss which was first studied by Sanctorius in 1614 and which is termed the *insensible perspiration* (a very small part of which is due to the slight excess in the weight of the carbon dioxide eliminated over that of the oxygen absorbed). The water lost in the insensible perspiration comes partly from the respiratory surfaces, but chiefly from the skin. In the absence of any activity of the sweat glands the surface of the avascular epidermis is kept slightly moist by water which reaches it from the extravascular fluid supplied by the capillary loops of the dermal papillae. When the heat loss by vaporization must be increased, the sweat glands become active and water may collect on the surface of the body in large and obvious amounts. Provided the conditions of the environment are such that evaporation of water can readily take place (low relative humidity) the amount of cooling of the body that can be effected in this way is very great. A man may exist without any marked rise in body temperature in a very hot environment even when he is exposed to an outside temperature that is the same as that of his body, or even greater. To encourage evaporation, however, he should be naked or very lightly clad, and the air should be kept in constant motion so that the layers of air next to the skin, which ordinarily very quickly become saturated with vapor, are transferred and replaced by drier air. Movement of the air also increases the heat loss by convection, provided the temperature of the air is not too near that of the body.

The stimulus to increased sweating has been thought to be dependent mainly on changes in the temperature of the blood since sweating does not immediately set in when the body is subjected to heat, as by a warm bath or a hot pack. It usually takes from ten to twenty minutes after the person has

been placed in the bath or surrounded by the warm blankets of the pack before sweating becomes pronounced. It has been shown, however, that the body temperature does not always need to be raised before sweating sets in. In a hot bath, sweating starts on the forehead before there is any change in rectal temperature and if the hand be plunged in cold water the sweating stops at once.

Loss of heat by evaporation of sweat occurs only in certain animals. It is practically absent, for example, in the dog and cat, where sweat glands occur only on the pads of the feet. The degree to which it may occur also varies in different individuals of the same species. The power of withstanding high temperatures is proportional in man to the facility with which he perspires. Where sweating is interfered with by skin diseases—by ichthyosis, for example—exposure to heat or increased heat production, as by muscular activity, may raise the body temperature to a dangerous degree.

Another factor upon which the efficiency of evaporation of sweat in cooling the body depends is the relative humidity of the air. When this is high, evaporation of water into it cannot occur, and it is on this account that an increase in body temperature is much more likely to occur in warm, humid atmospheres than in those that are dry. At the same temperature people can live in perfect comfort in the dry air of the open plains, but suffer immediately from rise of temperature when they go into the humid air of the river valleys. Similarly, work in hot factories or in mines is quite possible at very high temperatures if the air is kept dry and in motion, but becomes impossible when the air is moist. In judging the adequacy of air from this point of view, it is therefore important to take not the ordinary dry-bulb thermometer reading but that of the wet-bulb.*

In animals like the dog, which do not sweat over the surface of the body, *vaporization of water into the expired air* is the most important method of heat loss. Animals with heavy coats of hair which interfere with loss of heat from the skin are especially dependent upon this process. When such an animal is exposed to warmth the breathing suddenly becomes much quicker but not deeper (polypnea), the mouth is opened and the tongue executes to-and-fro movements which are synchronous with the movements of the tidal air. Panting is large dead space overventilation and it is effective chiefly because there is a coincident stimulation of the salivary and buccal glands which yield sufficient water for the increased vaporization. The more rapid movements of air through the mouth and upper respiratory passages and over the tongue also facilitate cooling by increasing the conduction of heat from the mucous membranes of these parts. The importance of the mouth and pharynx in the loss of heat by these means is shown by the finding that after introduction of a tracheal cannula a dog cannot withstand an increase of external temperature nearly as well as a normal animal.

The Relative Importance of the Chemical and Physical Methods of Control of Body Temperature.—This was accurately studied in the dog by Rubner. Both methods come least into play when the environmental temperature is not far from that of the body. As the former falls, physical regulation will at first alone suffice to maintain the body temperature. When a lower level is reached chemical regulation will also come into play. This has been very clearly shown (Table CIII) in a short-haired dog by measuring the caloric output (by the indirect method) at various environmental temperatures. It can be seen

*The wet-bulb thermometer registers a temperature that is lower than that of the dry-bulb in inverse proportion to the relative humidity of the air. When the air is completely saturated with moisture, the temperature recorded by the two instruments will be the same; when it is perfectly dry, the difference will be maximal.

TABLE CIII

TEMPERATURE	CAL. PER KG.	
7.6	86.4	Chemical regulation
15.0	63.0	
20.0	55.9	Physical regulation
25.0	54.2	
30.0	56.2	
35.0	68.5	Rise in body temperature stimulating metabolism

(After Rubner.)

that no change in energy production occurred as the environmental temperature fell from 30° C. to 20° C., alteration of heat loss from the surface being sufficient—physical control—but that below 20° C. the metabolism became augmented—chemical control. At temperatures above 30° C. the metabolism also increased, because physical control was no longer adequate to prevent

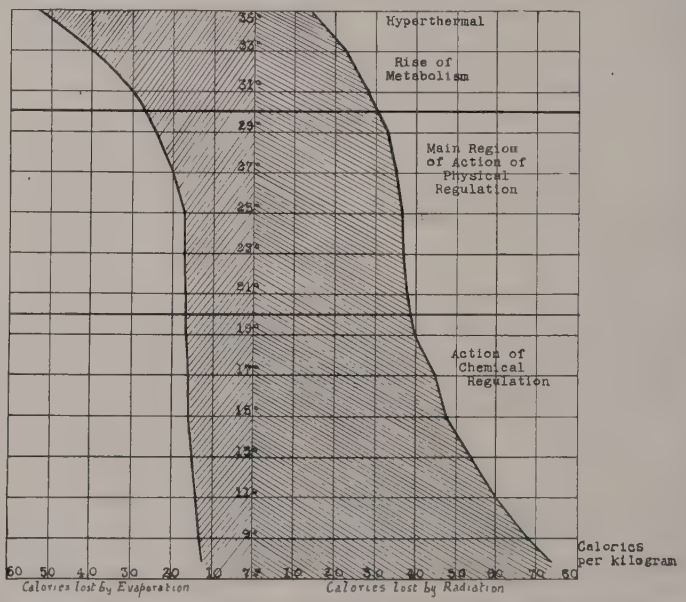


Fig. 319.—Rubner's chart showing the manner of heat loss at different room temperatures, in the dog. (From Lusk: *Science of Nutrition.*)

heating of the body and consequently an increase in all its chemical processes occurred. The temperature of 30° C. is hence styled the *critical temperature.* When the mechanism of physical control is upset in any way, chemical control sets in at a much higher temperature; for example, when the dog used in the above experiment had its fur shaved off, the caloric expenditure at 25° C. was 61.2 and at 20° C. it was 82.3. When there is a good layer of subcutaneous fat, the environmental temperature may be lowered considerably before chemical regulation sets in. Increased humidity at moderately high temperatures will increase metabolism because less heat loss can occur and the body becomes warmed.

These factors all play a role in determining the environmental temperature at which chemical regulation will become operative in man, but he has the advantage over other animals in that he can adjust his clothing to the environmental temperature. In studies[619] on a naked man in a calorimeter it has been found that when the environmental temperature lies between 22.7° and 34.5° C., the basal metabolism is surprisingly level and this fact suggests that the neutral range above and below which increased metabolism occurs may not be as narrow as is sometimes supposed. These experiments indicate that man has a very effective capacity to maintain a constant temperature over the range 23°-35° C., by adjusting heat loss alone.

The relative loss of heat caused by evaporation of water (in the expired air) and by radiation, etc. (from the skin) in the fasting dog is shown in Fig. 319, in which the abscissa gives the caloric losses by evaporation to the left and by radiation, etc., to the right of the vertical line about the middle of the chart, which also gives the environmental temperatures.

Baths also affect the energy output. They may induce a rise above the basal level not only when they are cold but also when they are very warm. This is shown in Table CIV.

TABLE CIV

	O_2 PER MIN. ML.	R.Q.
Normal	223.7	0.78
Hot bath at 42° C.	274.0	1.09
Normal	278.7	0.78
Cold bath at 17° C.	601.0	0.86

(Schapalo.)

The increase in the cold bath is, of course, due to chemical regulation of body temperature coming into play, whereas that in the hot bath is due to a warming of the tissues.

NERVOUS CONTROL OF BODY TEMPERATURE

The Part Played by the Innervation of Skeletal Muscle: "Thermal Muscular Tone" and Shivering.—Muscular activity is the main source of the heat produced by the body. In the discussion of the central nervous system it was emphasized that even at rest when no overt motion is taking place the muscles of the body are always exerting a certain small tension. This sustained activity or "tone" is due to low frequency discharges over motor fibers. It consists in a series of twitches or incomplete tetani in a certain fraction of the muscle fibers, but because the discharges in different motor neurons are asynchronous the muscle exerts a steady pull on its attachments. It is obvious that muscle tone is a continuous source of heat, and it has long been known that its abolition by curare or muscle denervation profoundly depresses the basal metabolic rate. We have seen how greatly muscular exercise increases heat production. But the central nervous system can make use of the great capacity of the skeletal musculature to produce heat without inducing locomotion or the other forms of overt bodily activity which we call muscular exercise. It does this by discharging impulses over motor fibers of the cerebrospinal system (not the autonomic system) in such a way that a tremor is produced. This activity

which we call *shivering* is specific in that it is evoked by exposure of the body to cold and on this basis may be differentiated from other forms of tremor.

The question has repeatedly been asked whether an increase in the tone of skeletal muscles, a response short of shivering, plays a part in the chemical regulation of body temperature. Burton and Bronk,[612] by studying the action currents of muscle, have secured some objective evidence of the occurrence of a true "thermal muscular tone." They found that in cats lowering of the body temperature below a critical level causes an increased muscular activity which precedes actual shivering and which, like ordinary muscle tone, is due to an incoordinated asynchronous twitching of the fibers of different motor units. This increased tone was found to begin with the first signs of a rise in metabolic rate. It was only later on continued cooling that this type of activity passed into the gross tremor of shivering which is brought about by the coordinated intermittent firing of motor units.

For years it has been held by one school of physiologists that increases in heat production in response to exposure to cold are due solely to increased muscular activity in the form of increased tone, shivering or actual exercise. The findings of Burton and Bronk are in harmony with this view. On the other hand, the two great pioneers in the field of metabolism, Voit and his pupil Rubner, held that some other factor or factors are involved in chemical regulation. We shall presently see that their surmise has received support in the shape of evidence that adrenalin, which has a calorigenic action, is secreted on exposure to cold. Already reference has been made (see page 865) to work which indicates that prolonged exposure to cold may lead to an augmented basal metabolism through increased thyroid activity.

The Part Played by the Autonomic Nervous System.—A consideration of the reactions which occur when the body temperature tends to rise or fall shows that with the exception of shivering "thermal muscular tone," alterations in respiratory movements and other responses in skeletal muscle all are mediated by the autonomic nervous system.

Only a few thermal responses are mediated by the parasympathetic division. Salivary secretion and secretion of the glands of the pharynx and respiratory tract, together with the local vasodilatation which accompanies this activity, are brought about by parasympathetic discharges. It is also possible that a small fraction of the cutaneous vasodilatation which occurs on exposure to heat is due to activity in this division of the autonomic. Doubtless some peripheral vasodilatation is mediated by impulses in dorsal root fibers, but, as we have seen (page 175), these are better classified as belonging to the cerebrospinal system than to the autonomic.

The greater part of the generalized thermal responses in visceral effectors is due to sympathetic control. Thus when environmental cold threatens to produce a fall in body temperature sympathetic activity leads to constriction of peripheral vessels, erection of hair (of feathers in birds) and liberation of adrenalin. The pilomotor activity serves to enmesh near the skin a layer of poorly conducting air; in the human being this response is signalled by the appearance of "goose flesh," a change signifying the survival of a reaction which was useful before the processes of evolution did away with most of man's body hair. The secretion of adrenalin is of service because of the thermogenic action of this hormone. Among the bodily responses to heat are sweating and

cutaneous vasodilatation. The former is due to impulses in cholinergic postganglionic sympathetic fibers, while the latter is to a very considerable extent accomplished by inhibition of the tonic discharge of impulses over sympathetic vasoconstrictor fibers. The contribution of specific sympathetic vasodilators to this response is possible.

The very great importance of the sympathetic system in the regulation of body temperature has been demonstrated conclusively by the study of animals in which total removal of the sympathetic chains has excluded all possibility of impulses reaching effectors over neurons of this system. As pointed out in Chapter XVI sympathectomized cats and monkeys remain in good health and show no abnormalities unless they are subjected to conditions of physiological stress. When such animals were first prepared and studied by Cannon and his collaborators[613] it was noted that they showed certain defects when confronted with the problem of maintaining a normal temperature in the face of environmental heat and cold. The sympathectomized cats "exhibited a marked antipathy to cold air and drafts. It has not been uncommon to see them literally spend days during the colder periods of the winter crouched on top of the warm-water heater and descending from it only at feeding times." In this they stood in marked contrast to the normal cats with which they were housed. When placed in a cold room the sympathectomized cats showed, in comparison with normal cats, a deeper depression of rectal temperature and a much greater frequency and prominence of shivering. Indeed, in such animals shivering appears to be the chief, if not the only, protection against a fall in temperature.

A study of the effect of high and low environmental temperatures on sympathectomized animals was later carried out in Cannon's laboratory by Sawyer and Schlossberg.[633] Table CV is from their report, and shows in a convincing manner the deficiencies of the animals without sympathetic pathways to visceral effectors. When normal cats are placed in a cold room at 8°-9° C. for three to four hours they exhibit occasional spasmodic shivering, show some erection of hair, and their rectal temperature usually rises slightly in evidence of an efficient control. Sympathectomized cats, on the other hand, behave quite differently. In them shivering begins at once and continues without interruption, but in spite of this powerful thermogenic response rectal temperature invariably falls. There is no erection of hair, and peripheral vessels fail to contract to the normal extent. Sympathectomized animals are also deficient in their response to environmental heat. Sawyer and Schlossberg found that normal cats placed in a hot room at 40°-41° C. for periods of from one to two and a half hours showed an average rise in rectal temperature of 1.40° C., while sympathectomized cats experienced an average rise of 2.25° C. The overt responses, such as panting and salivation, were more marked in the latter animals.

It has already been pointed out that the adrenal medulla is an integral part of the sympathetic system. Under ordinary quiet conditions of existence the secretory activity of this gland is at a standstill (page 171). Adrenalin is produced when conditions of stress cause a widespread and vigorous discharge of sympathetic impulses. Added to the blood as a result of a discharge of preganglionic sympathetic impulses, it supplements the action of postganglionic impulses throughout the body, but we know that this hormone exerts two effects

which apparently cannot be induced by the nerve impulses. These are increased tissue oxidations and the acceleration of the process whereby liver glycogen is converted to blood sugar. Both, more especially the former, are of importance in temperature regulation. The role of medulliadrenal secretion in the chemical control of body temperature was demonstrated by Cannon, Querido, Britton and Bright.[614] Surviving healthy cats in which the heart had

TABLE CV

RESPONSES OF NORMAL AND SYMPATHECTOMIZED CATS TO EXPOSURE TO A LOW ENVIRONMENTAL TEMPERATURE (From Sawyer and Schlossberg[633])

CAT	DATE 1932	BODY TEMPERATURE BEFORE ENTERING COLD ROOM	TIME IN COLD ROOM		TEMPERATURE OF COLD ROOM	BODY TEMPERATURE JUST AFTER LEAVING COLD ROOM	MAXIMAL CHANGE IN TEMPERATURE WHILE IN COLD ROOM	BEHAVIOR IN COLD ROOM
					Normal control cats			
		°C.	*hours*	*minutes*	°C.	°C.	°C.	
88	April 15	38.20	2	00	8.00	38.40	0.15 (rise)	Slight shivering, hair rising
30	April 15	38.55	2	00	8.00	38.75	0.20 (rise)	Slight shivering, hair rising
27*	April 19	39.10	2	50	9.00	38.45	0.65 (fall)	Hair standing, shivering
49	April 25	38.10	4	45	8.00	38.50	0.40 (rise)	No shivering
45	April 25	39.10	4	50	8.00	39.20	0.11 (rise)	Slight shivering
30	April 25	38.00	4	00	8.00	38.65	0.65 (rise)	Slight shivering
					Sympathectomized cats			
99	April 15	38.35	2	00	8.00	37.50	0.85 (fall)	Marked shivering
95	April 19	38.90	2	05	9.00	37.50	3.60 (fall)	Marked shivering
94	April 19	38.65	1	55	9.00	37.40	1.30 (fall)	Shivering
99	April 25	38.55	4	00	8.00	37.80	0.80 (fall)	Shivering and temperature starts to go up; has fever next day
95	April 25	38.10	4	00	8.00	35.90	2.35 (fall)	Shivering
96	April 25	38.35	4	05	8.00	37.45	0.80 (fall)	Shivering throughout
91	May 17	38.55	4	00	9.00	37.20	1.35 (fall)	Shivering throughout
89	May 17	38.40	3	00	9.00	35.95	2.40 (fall)	Marked shivering
97	May 17	39.05	3	45	9.00	38.35	0.70 (fall)	Shivering (angry when temperature taken)
95	May 17	38.40	4	00	9.00	37.55	1.40 (fall)	Shivering
90	May 17	38.40	2	30	9.00	36.00	2.40 (fall)	Shivering

*Cat developed snuffles next day.

been denervated showed marked accelerations of the pulse rate when exposed to cold. The same phenomenon occurred when a heat debt was established by introducing a known amount of cold water into the stomach. After removal of one adrenal gland and denervation of the other the same procedures caused either slight accelerations, no change, or a moderate decrease in heart rate. As a result of these experiments it was concluded that an increased discharge of adrenalin occurs under circumstances which tend to lower body temperature. The evidence that secreted adrenalin is of service under these

conditions by virtue of its calorigenic action rests on the observation that when the adrenals are inactivated by denervation shivering becomes much more prominent. A moderate heat debt may be met successfully by a normal animal without shivering, but after adrenal inactivation the establishment of the same debt results in prompt and long-continued shivering. Cannon and his collaborators also studied the effects of a heat debt on a number of human subjects. It was found that debts averaging 449 small calories produced a rise in oxygen consumption which averaged 16.4 per cent. Since these increases were not accompanied by shivering, it was inferred that they were due to some factor other than muscular activity, presumably stimulation of metabolism by adrenalin. It is possible, however, that an imperceptible increase in the tonic contractions of skeletal muscle occurred. In any event, the animal experiments show clearly that when adrenalin is discharged on exposure to cold shivering is less marked. It is hard to avoid the conclusion that, by virtue of its calorigenic effect, secreted adrenalin is a real factor in the control of body temperature.

The Central Nervous Control of Body Temperature.—All the changes in the body which normally act in the face of changes in environmental temperature to preserve a relatively constant temperature are due to an increased or decreased number of impulses in cerebrospinal and autonomic nerves. Since these alterations in impulse discharge are of central origin we must search in the central nervous system for the mechanisms which execute the delicate control outlined in the preceding paragraphs of this chapter.

In the case of man the body temperature is to a considerable extent under voluntary control. By the choice of clothing and the artificial heating and cooling of habitations we supplement the involuntary management of heat loss. Similarly, we may aid the chemical control of body temperature by voluntarily increasing or decreasing our muscular activities. It is, of course, most fortunate that we do not have to rely entirely on voluntary adjustments to secure and maintain the necessary thermal environment for our body cells. Were that the case, it is obvious that little time or strength would be left for any other endeavor. The essence of the matter is that if the processes of phylogeny had failed to develop an automatic thermotactic device in the central nervous system of birds and mammals, these animals could never have attained that freedom from environmental influences which distinguishes them from the cold-blooded amphibian and reptile.

When the spinal cord is transected in the cervical region, body temperature quickly falls unless it is artificially maintained. The extent to which the animal or man comes to behave as if cold-blooded, after cord section, varies somewhat with the level at which the cut is made. If it is in the upper thoracic region, for example, the regulation against cold, although distinctly less efficient than normal, is far better than when the secton is made through the cervical cord. The difference is largely dependent on the fact that after the lower section much larger muscle groups and skin areas are left innervated from the brain, but preservation of the cerebral connections of the uppermost portion of the sympathetic outflow is also a factor.

In dogs long surviving spinal transection and entirely free from symptoms of spinal shock Sherrington[634] showed that there is in the region innervated from behind the lesion marked failure of vasomotor responses to even great changes in environmental temperature. Shivering does not occur as a spinal reflex no matter how considerable the exposure to cold, and Sherrington was unable to induce sweating to heat in the paraplegic regions of his dogs.

The dependence of normal thermal responses on prespinal central mechanisms is strikingly illustrated by the appearance of shivering in the muscles innervated anterior to the level of a spinal section when the parts below are immersed in cold water. Sherrington found that "the nonappearance of cold shivering in the paraplegic region of the dog can reveal with great clearness the exact segmental level of the spinal lesion by demarcating the muscle-field innervated behind the lesion from that in front. The boundary so shown will actually subdivide an individual muscle, e.g., the anterior part of deltoid will shiver violently while in its posterior part no shivering can be evoked." If the transection is at or above the 7th cervical segment and the room temperature is kept at its usual level, the shivering in the anterior parts of the body is not accompanied by any signs of cutaneous vasoconstriction. The forefeet and ears remain warm to the touch because of the separation of the sympathetic outflow from prespinal centers. With a midthoracic transection the response to cooling the hindparts includes vasoconstriction. These reactions in regions not directly exposed to environmental cold and yet separated from the cooled parts by cord transection may be reflexes evoked from the sentient parts by cold blood from the chilled region or they may be the results of a direct effect of cooled blood on the thermotactic mechanisms of the brain. The operation of the latter possibility is rendered plausible by the observation that localized cooling of the brain stem causes shivering and vasoconstriction (Barbour[609]).

Certain investigators have claimed that after complete low cervical transection of the cord various experimental animals and even man may show a considerable capacity to regulate body temperature (for an excellent critical review of this subject see Ranson[631]). Recently G. Clark[616] has reported the results of a careful study of cats which were maintained in excellent health for long periods after complete section of the lower cervical cord. While confirming the results obtained by Sherrington *(vide supra)* he has been able to throw light upon some of the claims to which allusion has just been made. Clark found that after his cats had been subjected for weeks at a time to a relatively low environmental temperature (about 70° F.) they were able to maintain a higher body temperature on exposure to cold than before this treatment. He concludes that while such preparations are "unable to make the adjustments necessary for maintaining a normal body temperature when there occurs a sudden and considerable fall in environmental temperature" they may develop a slow adjustment to cold, an acclimatization. Since this change is not accompanied by any capacity to shiver in muscles innervated from below the transection or to vasoconstrict or erect hair in any region of the body, and since no signs of chronic vasoconstriction were evident, Clark suggests that the animals develop, as a result of exposure to low temperatures, an increase in the basal metabolic rate. He finds that the greater ability to withstand cold is lost if the animals are kept again in a warm environment. Ranson[631] has suggested that this slow and very limited temperature regulation which is evidently humoral in origin may be referred to increased thyroid activity. In the light of Uotila's results (see page 865) it would be interesting to know whether it depends on the integrity of the pituitary stalk.

Studies on spinal animals show conclusively that *the essential heat regulating machinery of the central nervous system has a prespinal localization.* It remains to consider the delimitation or distribution of this. That the decerebrate cat or dog is essentially poikilothermic is a fact universally admitted. Even when such preparations are kept alive for several weeks, as in the experiments of Bazett and Penfield (see page 136), they display no effective thermoregulatory responses. After any mesencephalic transection of the brain in carnivores shivering cannot be induced by cooling either the skin or the entire body, and the only respiratory response to heating is a slow increase in the

rate of breathing from a normal frequency of 16-40 a minute to 90 or less. True panting in the sense of to-and-fro movements of the tongue and labial commissures with mouth open and at a rate of 200-375 a minute is never seen. The heat-regulating center or centers of the higher mammals must reside somewhere above the midbrain, i.e., in the diencephalon, corpora striata, or cerebral cortex.

The literature on the subject of temperature control which appeared before the year 1912 is filled with assertions that the corpora striata are essentially concerned in this function. But most of the experimental evidence put forward in support of this contention was open to various interpretations and signified little; the work consisted chiefly in making mechanical or chemical injuries in the striata and noting transient hyperthermias. At the end of this period Barbour[609] made the significant discovery that in the rabbit cooling or heating the region of the corpora striata induces marked thermal responses: heating produces faster breathing and vasodilatation, while cooling gives generalized vasoconstriction in the skin and shivering with an increase in oxygen consumption. In the light of subsequent work it seems certain that Barbour's results were due to alterations in the temperature of the *hypothalamus,* which of course lies at no great distance from the corpora striata. As we shall see, this ventral division of the diencephalon is without question the part of the brain most essential for temperature regulation.

Ott in 1887 first placed emphasis on the hypothalamus as a region of the brain concerned in temperature control, but his observations had little influence on contemporary workers. It was in 1912 that Isenschmid and Krehl,[623] working on rabbits, first furnished acceptable evidence that after removal of the cerebral cortex and corpora striata an animal retains a nearly normal ability to regulate its body temperature throughout a wide range of environmental temperatures. Since rabbits in which all the brain down to the mesencephalon had been removed were found to possess no ability to regulate, it was concluded that the diencephalon contains the temperature regulating center. Other experiments, which were continued by Isenschmid and Schnitzler,[624] indicated that in the rabbit the tuberal region is the essential portion of the diencephalon, as far as temperature regulation is concerned (see Chapter XVII). Much later other investigators (Keller and Hare,[625] Bazett, Alpers and Erb,[610] and especially Ranson and his collaborators[631, 632]) showed conclusively that the hypothalamus is the one part of the brain which is absolutely essential for normal temperature control. There is evidence that with the exception of certain parts of the cerebral cortex no portion of the brain lying above the hypothalamus plays any important role in temperature regulation. Pinkston, Bard and Rioch[630] studied the responses to changes in environmental temperature in a number of long-surviving cats and dogs which had been deprived of neocortex and additional portions of the forebrain. It was found that animals lacking cortex, striatum, and all of the diencephalon except the hypothalamus and the most medial portion of the thalamus regulate in the face of extremes of cold and heat just as efficiently as do animals which are merely decorticate. Moreover, these animals showed only relatively minor disturbances of temperature regulation when compared with normal controls. On the basis of functional tests and histological studies of serial sections of the brains, it was concluded that in the decorticate animal the striatum, the lateral basal olfactory areas and pos-

sibly the rostral two-thirds of the midline groups of thalamic nuclei play no significant role in temperature regulation.

The evidence that the hypothalamus contains the most important central mechanisms for temperature regulation has been very considerably strengthened and extended by Ranson and his collaborators (see Ranson and Magoun[632] and Ranson[631]). The general conclusion has been reached that there are two rather distinct and anatomically separate thermo-regulatory mechanisms in the hypothalamus, a rostrally situated one which prevents overheating and a more caudally located mechanism which protects the body against chilling. By placing well-circumscribed electrolytic lesions in different parts of the brain stems of cats and monkeys Ranson and his associates have demonstrated that injuries limited to the caudal portion of the hypothalamus (bilateral lesions dorsolateral to the mammillary bodies), which leave the rest of the brain intact, produce a permanently poikilothermic condition. Although ordinary motor activity is not impaired, the animals fail to sweat or pant when warmed and do not shiver when cooled. On the other hand, when the tissue lying above and in front of the optic chiasm and below the anterior commissure (the preoptic and supraoptic regions—see Fig. 69, page 188) is destroyed the animal is no longer able to protect itself from overheating—on exposure to warmth a cat with such a lesion fails to pant or sweat and consequently develops a hyperthermia—but it shows little or no impairment of its capacity to regulate against environmental cold. Further evidence that this rostral portion of the hypothalamus is prepotent in bringing about heat loss was secured by Magoun, Harrison, Brobeck and Ranson[626] who examined the effects of locally heating various parts of the hypothalamus by passing a high frequency alternating current of low voltage between the tips of two electrodes inserted into the brain; such a current warms but does not electrically stimulate the tissue through which it passes. It was found that panting and sweating could be far more readily obtained by warming the area between chiasm and anterior commissure than any other part of the hypothalamus. The study of the effects of lesions showed that the descending pathways through which this mechanism for heat loss acts run backward through the lateral hypothalamic areas (see Fig. 69, page 188).

As already intimated the hypothalamic mechanisms which protect the body against environmental cold by causing heat formation (e.g., by shivering) and inducing heat conservation (by vasoconstriction) are to a considerable extent separate from those involved in regulation against heat. On the whole they lie more caudally. They are not seriously impaired by hypothalamic lesions of moderate size unless these are bilateral and located in the caudal part of the lateral hypothalamic area so as to destroy much of the tissue between the mammillary bodies and the cerebral peduncles. Ranson[631] has concluded that the neurons which constitute the chief central mechanism for protection against cooling are "distributed through a large part of the hypothalamus and are perhaps in part at least identical with those which are responsible for vasoconstriction and piloerection and some other sympathetic functions." The fact that stimulation of the hypothalamus evokes a widespread sympathetic discharge was mentioned in Chapter XVII. And there it was pointed out that the significance of this experimental finding probably lies in the fact that general bodily functions which involve sympathetic activity, functions such as

temperature regulation and the expression of certain forms of emotional excitement, rather than the sympathetic system itself, are integrated at the hypothalamic level.

Although there can be no doubt about the indispensability of the hypothalamus for temperature control, it would be a mistake to conclude that it contains the only neural mechanism concerned in this regulatory function. The hypothalamus must exert its effects through the autonomic and somatic centers of bulb and cord. There is also evidence showing that cortical mechanisms are concerned in temperature regulation. It is well known that vasomotor changes are induced by stimulation or ablation of cortical tissue (see page 186). Removal of the frontal pole of one cortex in the dog produces in the contralateral side of the body chronic cutaneous vasodilatation with failure of the skin vessels to constrict normally on exposure to cold.[630] In the monkey a comparable lesion causes vasoconstriction (Kennard).

Complete decortication in carnivores (cats and dogs) does not seriously impair temperature regulation, but the results observed by Pinkston, Bard and Rioch[630] in long surviving animals show that this part of the brain exerts some influence on the processes of temperature control. In addition to the vasomotor effects just mentioned dogs without neocortex and with subsequent secondary degeneration of the thalamus showed the following changes in their thermal responses: a very delayed slow hyperpnea in response to conditions that promptly induced true panting in the same animals before operation; a rise in rectal temperature before hyperpnea developed (normal dogs show polypnea without any rise in rectal temperature); and immediate vigorous shivering in response to cold, frequently producing a rise in body temperature, whereas before operation the same animals showed the usual delayed and less marked reaction with a fall in body temperature. Cats with equivalent lesions behaved in a similar manner, but showed no disturbance of the panting response, which in this species is not as highly developed as in dogs. It should be emphasized that all these animals, whether lacking only cortex or deprived of practically all cerebral tissue above the hypothalamus, maintained normal body temperatures under ordinary laboratory conditions and withstood exposure to heat (37.5° to 41.4° C.) and cold (15.0° to 0.6° C.) for as long as four hours with relatively small changes. The disturbances they showed were in the details of regulation, and some were overreactions (e.g., excessive shivering). Whether the cerebral cortex exerts its influence through the hypothalamus or directly on bulbospinal centers is not known. Finally, we may be sure that in man, where the general process of corticalization of function has reached its fullest expression, the cerebral cortex exerts a very much greater influence on temperature regulation than in the lower mammals which, of necessity, have been the subjects of experimentation in this field of neurophysiology. There are, however, a number of clinical studies (see Davison and Selby,[618] and Davison[617]) which indicate the importance of the hypothalamus in the regulation of temperature in man.

The processes of temperature control may be set into action in one or both of two ways. Reflex responses are evoked by the effect of heat or cold on receptors. The best known examples of this are the vascular changes which occur in unexposed skin areas the moment another area is heated or cooled. Normally panting in the dog is this type of response. A dog will pant on slight cutaneous warming, and without the slightest rise in rectal temperature. Indeed he may continue to pant when the response has caused rectal temperature to drop below normal, provided the skin is locally warmed. This was designated

"reflex panting" by Richet, who discovered its nature. It does not occur in dogs under anesthesia. "Central panting," on the other hand, is a form of the response which Richet considered to be the result of warming of the nervous centers in the brain by heated blood. It is seen in anesthetized dogs, and a rise in rectal temperature is required for its occurrence. The observation that panting may be evoked by warming the carotid blood or by direct application of heat to the rostral hypothalamus (see above) indicates the correctness of Richet's view as to its nature. Doubtless all thermal responses could be classified as reflex or central or both. Panting in the cat is always "central" in the sense that it never occurs normally unless there is a rise in rectal temperature.

Fever

The clinical application of a knowledge of the mechanism of heat regulation in the animal body concerns the causes of fever. Recently the artificial production of fever for therapeutic purposes has added still further to the clinician's interest in the subject. In its most familiar form fever is produced by infectious processes, but it may also be due to various other causes, among which may be mentioned the parenteral injection of foreign protein, excessive destruction of protein substances in the body itself, the action of certain drugs, and lastly, injury to various portions of the brain. Several types of fever are recognized: when the temperature remains constantly above the normal, it is known as continuous fever; when oscillations occur but the temperature never falls to the normal level, it is known as remittent; when it attains the normal level at certain periods during the day, it is known as intermittent.

The Mechanism of Fever.—During a *sudden rise* in body temperature there is, on the one hand, increased heat production in the muscles, and on the other, diminished heat loss from the surface of the body. *The fever is therefore due to an exaggeration of the processes by which the body normally reacts to conditions which tend to lower the body temperature.* Shivering may occur, and the constriction of the cutaneous blood vessels produces the subjective sensation of chills, causing the skin to become pale and cold to the touch. The skin muscles also contract, producing "goose skin." During this stage, objective demonstration of the curtailment of the skin circulation becomes possible by observation of the blood flow through the hands and feet. When the temperature *suddenly falls* again (the crisis, as it is called), the muscles become flaccid and produce less heat, and the cutaneous blood vessels dilate, as can also be shown by measurements of the blood flow of the hands and feet. At the same time also, the sweat glands are stimulated and marked perspiration occurs.

Concerning *the cause of continuous fever,* it must be assumed that the balance between heat production and heat loss has been adjusted at a higher plane than normal. We cannot explain the fever on the basis either that heat production alone is increased or that heat loss alone is diminished, for in neither of these cases would the temperature stand at a permanent level. The thermoregulatory nerve centers, while set at a higher plane in fever, are still capable of responding in the usual way to the influences which cause the body temperature to change in a normal person. For example, when a fever patient is subjected to a hot bath so that his body temperature rises about 0.2° to 0.5° C., sweating occurs just as in a normal individual; or if exercise is taken the increased amount of heat thereby produced in the muscles is dissipated in the usual way. When, on the other hand, the patient is exposed to cold, the vessels of the skin contract and he shivers.

Although fever is not caused by an actual disturbance of the balance between heat production and heat loss, neither of these processes is proceeding at its normal rate. That there is a distinct increase in the total heat production of the body in acute fevers in well-developed persons has been shown by means of the respiration calorimeter. This increased heat production is not observed in patients who have been brought into a weakened condition and in whom the muscular tissues have become atrophied by long-continued fever.

It is particularly during the chill preceding a fever that the basal metabolism is increased. At the onset of an attack, in malaria for example, the caloric expenditure may be increased two or three times over the normal. This is related to the shivering, for it occurs also when this is brought on by a cold bath which may cause it to increase 180 per cent. During the continuous fever, of typhoid for example, the increased metabolism is proportional to the rise in rectal temperature and in a general way van't Hoff's law holds, namely, that the chemical activities (metabolism) of the body increase from two to three times for every rise of 10° C. in rectal temperature. This means that the caloric output increases by about 7 per cent for each degree Fahrenheit through which the rectal temperature is raised. These relationships are also evident in the fever which follows intravenous injection of proteose or typhoid vaccine. The increased heat production in continuous fever is mainly dependent upon the increase in body temperature and is not one of its causes, as is evident from the fact that far larger quantities of heat are frequently produced in normal individuals as a result of muscular exercise or the taking of large quantities of protein-rich food. The heat thus produced is, however, very quickly dissipated, so that only a temporary rise in temperature occurs. A large heat production also occurs in hyperthyroidism without a corresponding rise in body temperature.

Similarly, it can be shown that in continuous fever there is a relative inefficiency in the mechanism of heat dissipation. When the temperature of a normal person is artificially raised through about 1° C., a marked increase in cutaneous blood flow and profuse perspiration are invariably noted. In a patient with fever of the same degree, on the other hand, there is practically no change in the skin circulation; indeed, it is usually diminished, and there is no unusual perspiration. The heat-regulating mechanism is now fixed on a plane that is higher than the normal, so that although further increase in body temperature, as we have seen, calls forth responses like those in a normal individual, yet at the fever temperature itself there are none of the reactions which a normal individual would exhibit if his temperature were artificially raised to that level.

The adjustment of the temperature at the higher level is by no means so perfect as it is at the normal level of health, so that a normal subject is more resistant to the effects of cold than is a patient with fever. The degree of response of the fever patient, however, varies considerably from time to time; a cold bath in typhoid fever, for example, lowers the body temperature much less effectively at an early stage in the disease, when the fever is more or less continuous, than later when it is becoming of the intermittent type. In the third week of the disease the cold bath more readily brings down the temperature and keeps it down for a longer time than during the first or second week. The mechanism for heat loss is also deranged in fever, which explains the rise in tem-

perature that is likely to follow the performance of even moderate muscular exercise or the taking of too hearty a meal in tuberculous or convalescent typhoid patients.

Changes in the Body During Fever.—In seeking the cause of fever which is evidently of an obscure nature, it is necessary to collect all the information we can regarding the metabolic changes that are then occurring in the animal body. A few of the most significant facts that have so far been collected may be mentioned here. Some of the most important concern the disturbance in nitrogenous equilibrium caused by the considerable loss of nitrogen which takes place in fever patients when they are fed on the usual hospital diet prescribed for such cases. This loss of nitrogen is no doubt the result of the partial starvation in which the patient is kept; for it has been shown that patients with typhoid fever may be maintained in nitrogenous equilibrium by feeding them with relatively large amounts of carbohydrate, which acts by protecting the protein of the body from disintegration. The protein minimum to which fever patients can be reduced is nevertheless considerably higher than the minimum in normal individuals.

From the above results as a whole, it is probably safe to conclude that there is *a specific destruction of protein* going on in the body during fever. Further evidence of such a destruction is furnished by the presence in the urine of excessive amounts of creatinin, of purine bases, and, it is said, of incompletely hydrolyzed proteins, such as the albumoses (proteoses). Moreover, when the fever suddenly terminates in crisis, there is a marked increase in the excretion of urea (the epicritical urea increase), which indicates that an extensive deamination of protein building stones (amino acids) is occurring. The so-called "diazo reaction" obtained in the urine during the fever is also believed to depend on the presence of abnormal protein-disintegration products. As to the specific cause of the increased protein disintegration, little is known.

Although there is increased protein breakdown during fever, it must not be forgotten that when food is refused only about 20 per cent of the total expenditure of the body is derived from this foodstuff, 80 per cent coming from non-nitrogenous material, which must be fat, because the available carbohydrates are used up at an early stage.

Since the general metabolism is increased, the excessive breakdown of the fatty substances, occurring as it does in the presence of a diminished combustion of carbohydrates, interferes with the proper oxidation of the fatty-acid molecules and leads to the appearance of so-called acidosis products in the urine, and consequently to a relative increase in the urinary ammonia. *A tendency to acidosis* therefore exists. The acidosis may reach a considerable degree of severity and cause the tension of carbon dioxide in the alveolar air to become diminished.

Another interesting metabolic change in fever concerns *the salt balance.* This is studied by observing the amount of sodium chloride excreted by the urine. As is well known, this becomes markedly diminished until the crisis of the fever, when it suddenly increases. The salt retention is related to the concentration of the blood, a marked rise in which is usually accompanied by a rise in temperature and is an unfavorable prognostic sign. Salt retention is more marked in certain types of fever than in others, and it is essentially different in nature from the salt retention that has been observed to occur in nephritis. This difference has been brought to light by examination of the chloride content of the blood. In nephritis, the concentration of chlorides in the blood is considerably increased, whereas in fever it is markedly diminished. The deficiency in salt elimination cannot be attributed to a deficiency of salt in the food, for it sets in before the diet has been curtailed and, when salt is given to a febrile patient, it is retained in the body to a greater degree than is the case in the normal individual.

Belonging to this group of fevers must also be considered the important ones produced by the intravenous injection of certain forms of protein, as those of egg white or those derived from the bodies of bacteria or from the laked corpuscles of a foreign blood. The fever in these cases is without doubt caused by a mechanism closely related to that responsible for anaphylaxis. It is believed that many cases of so-called aseptic fever, occurring after severe contusions or other wounds, may be the result of destruction of proteins within the body. Similarly the rise in temperature during infections may be attributable to the breakdown of protein by microorganisms within the cells.

Nervous Factors in the Production of Fever.—Since fever is essentially the result of an exaggeration of the processes which the body normally uses to prevent a fall in temperature, we may expect to find in action those nervous mechanisms which bring about decreased heat loss and increased heat production.

Pinkston[628] has reported that the febrile reaction in rabbits which results from the injection of typhoid-paratyphoid vaccine causes a marked constriction of the blood vessels of the normally innervated ear. The response normally begins very soon after the injection, and persists until the peak of the temperature rise has developed. He found that when the sympathetic supply to one ear was cut, constriction occurred there in only one-half of the cases. In some of these it occurred immediately after injection of vaccine; in others the response came on only after a delay of one to three hours. The former type

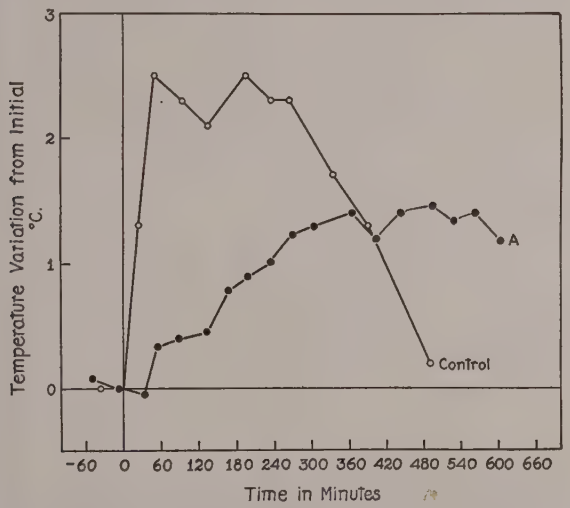


Fig. 320.—Representative fever curves from a normal cat (Control) and from a cat (A) in which both sympathetic chains had been removed from the stellate ganglia to the fifth lumbar ganglia, inclusive. Typhoid-paratyphoid vaccine injected intravenously at 0 time. (From Pinkston: Am. J. Physiol. 111: 539, 1935.)

of reaction was abolished by inactivation of the adrenals, which indicates that fever may cause a liberation of adrenalin. The delayed response shown by some of the animals was not affected by adrenal inactivation and is of unknown origin. In a second study Pinkston[629] obtained evidence that sympathetic activity in general accounts for a considerable fraction of the fever evoked by injection of vaccine. In this work cats were used. After complete interruption of all sympathetic impulses to effectors had been carried out by removal of both lateral chains of ganglia, there was a pronounced delay in the onset of the febrile reaction and in the attainment of the maximal increase (Fig. 320). When only the splanchnic outflow was left intact, the sympathetic supply to the periphery being destroyed, the fever curves were similar to those yielded by completely sympathectomized animals. On the other hand, the

curves obtained with cats with only the splanchnic nerves sectioned or with adrenals inactivated were only slightly different from those of normal cats. Previously Cannon and Periera (1924) had obtained evidence that secretion of adrenalin occurs in fever. If this is so, some of the rise in temperature may be due to its calorigenic action. Pinkston's results do not exclude this possibility, but they especially emphasize the part played by sympathetic vasoconstrictor impulses to the skin. It is obvious that when the latter are excluded, heat loss from the skin delays the onset of fever, causes the temperature to rise more slowly, and prevents the attainment of the usual maximum (Fig. 320).

Significance of Fever to the Organism

It is impossible at present to state definitely whether fever is a reaction of the organism against infection and therefore of benefit in assisting the organism to combat it, or whether it is in itself an unfavorable condition. The question can certainly not be answered by observing the behavior of bacteria growing at different temperatures in various media outside the body. That certain bacteria should be found not to thrive at incubator temperatures equal to those found in the body during fever, does not at all prove that this fever is of significance as a means of combating the growth of the bacteria in the body. It is undoubted that, where the body temperature becomes excessively high, the correct treatment is to keep it down as much as possible. On the other hand, the reduced mortality that has followed the introduction of the cold-bath treatment in typhoid fever may not be due so much to the reduction in body temperature itself as to the favorable effect produced on the nervous system and circulation. We certainly know that in normal animals moderate degrees of hyperpyrexia brought about by exposure to moist heat are well borne for considerable periods of time, thus indicating that it is the infection and not the hyperthermia that causes the serious damage to the body in infectious fevers.

PART VI

THE PHYSIOLOGY OF THE ALIMENTARY TRACT

By George R. Cowgill

CHAPTER LX

FUNDAMENTAL PHENOMENA OF GLANDULAR ACTIVITY

For the body to maintain itself it is necessary to ingest food. Materials which can serve as food must be capable of passing into the substance of the body itself. Some food materials are readily absorbed whereas others require certain chemical changes in their molecules before they can be utilized. The process by which these substances are thus prepared for actual use by the organism is called digestion. The organs which function in relation to this process are those of the alimentary tract. It is not our purpose here to discuss the detailed chemistry of food materials. This will be found in the section on Metabolism and Nutrition. It is pertinent to our present theme, however, to point out that chemical analysis alone does not necessarily suffice to determine whether a given substance can serve as a food. For example, the organic chemist regards starch as a polysaccharide which yields glucose on hydrolysis. To the student of alimentation, however, a starch, to be a food, must be capable of undergoing this hydrolysis to yield glucose *within the alimentary tract*. In other words, there is an inherent, purely biological factor which must be considered before one can say that a given complex substance is truly a food. The organs of the alimentary tract are the ones particularly concerned in the physiological operation of this biologic factor. It is our purpose here to discuss the functioning of these organs.

It will be convenient to consider, first of all, certain properties that are common to the digestive glands, and then the conditions under which each gland functions during digestion.

MICROSCOPIC CHANGES DURING GLANDULAR ACTIVITY

Structurally the active part of the glands, represented by the acinus or tubule, is composed of a basement membrane lined internally with the secreting epithelium. Outside the basal membrane are the lymph spaces and blood capillaries. The process of secretion involves fundamentally the passage of certain raw materials from the blood and lymph through the capillary wall into the lymph spaces and then through the membrane of the epithelial cell into the cell interior; there certain chemical and physical changes occur resulting in the elaboration of substances characteristic of the secretion of that cell and the discharge of them along with other materials not peculiar to the secretion alone, such as water and electrolytes, for example. As in many other physiological processes, there are

obviously two phases of the secretion process to be considered, one which covers the changes occurring when the cell is resting, or preparing for a later period of activity, and the other dealing with the phenomena of active elaboration and discharge of the secretion.

After the gland has been at rest, the cells become filled with granules or small globules, which are often so numerous as almost entirely to obliterate the nucleus. When the gland becomes active, on the other hand, the granules or globules leave the cells, except for a few which remain toward the lumen border

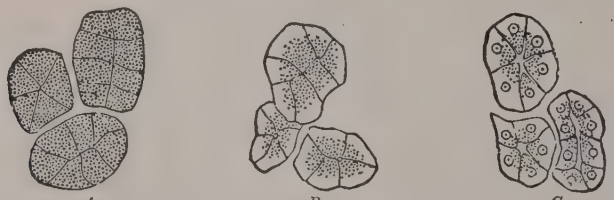


Fig. 321.—Cells of parotid gland showing zymogen granules: *A*, after prolonged rest; *B*, after a moderate secretion; *C*, after prolonged secretion. Note that prolonged secretory activity is associated with marked decrease in the number of zymogen granules. (From Langley.)

Fig. 322.—Parotid gland of rabbit in varying states of activity examined in fresh state. The upper left-hand acini are resting. The upper right-hand acini are from a gland stimulated to activity by injecting pilocarpine, and the two lower acini from one after stimulation of its sympathetic nerve. (After Langley.)

(Figs. 321 and 322). These observations indicate that the granular or globular material must represent part at least of the secretion of the glands. Sometimes, before they are extruded, the granules become changed in some way, as is indicated by the fact that they stain differently from those of the resting gland. It must not be thought, however, that an extrusion of granules *necessarily* accompanies secretory activity, for under certain conditions a copious secretion of water and inorganic salts, as well as a certain amount of organic material, may be produced without any change in the arrangement of the granules. In such

cases it has been observed, as in the pancreas, that fine channels develop in the protoplasm of the cell (Fig. 323).

From this histological evidence it would appear that the gland cell during rest is endowed with the property of building up out of the protoplasm, as granules or globules, the material which is to serve as one of the main organic constituents of the secretion. It is commonly believed that this is the precursor of the active ferment of the secretion; hence, its name, *zymogen* (leaven + producer). It has been shown that the process of separation of the zymogen granules starts around the nucleus with the production of a basophile substance, which in hardened specimens sometimes takes the form of filaments. From this basophilic *ergastoplasm* (to work + plasm), as it is called, the granules are gradually formed, and for some time continue to undergo slight further changes, as is

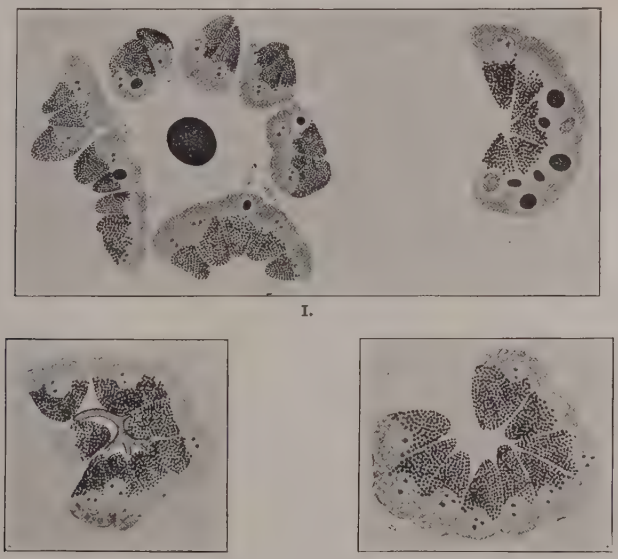


Fig. 323.—Three preparations of pancreatic acini stained by eosin orange toluidin blue. The acini of I were from a gland after vagus stimulation, and it is noted that besides free extrusion of the granules, globules staining with orange (and appearing in deep black in the photograph) have formed and may be present in the ductules. Some of the globules, however, change in their staining properties, becoming light red (dark gray in photograph). The acini in II and III were from glands excited by secretin. No globules appear; the granules remain, and fine canaliculi appear in the clear protoplasm. (From Babkin, Rubaschkin and Ssawitsch.[10])

evidenced by the fact that the staining reaction of those near the base of the cells differs from that of those at the free margin. When the gland cell is excited to secrete, the granules before being extruded, as noted above, often undergo a definite change, becoming swollen and more globular in shape.

MECHANISM OF SECRETION

These microscopic studies merely tell us that active changes, associated with the production and liberation of certain of the constituents of its secretion, are occurring in the gland cell, but they throw no light on the mechanism whereby

the gland cells secrete *water and inorganic salts*. This may be dependent, to a certain extent at least, on differences in osmotic pressure. A possible explanation of the flow of water is as follows: If a watery solution of some osmotically active substance is put in a tube, which is closed at one end by a membrane impermeable to this substance and at the other by one permeable to it, and the tube immersed in water, a continuous current will be found to issue from the permeable end so long as there remains any osmotically active substance in the tube. If we assume, then, that the membranes at the two ends of the secreting cell are of such a nature that the one next the basement membrane is impermeable to some osmotically active substance manufactured by the cell, and the other toward the lumen is permeable, it will be clear that, so long as this substance exists in the cell, it will attract water from the blood, and the water together with the osmotically active substance will be discharged into the lumen.

The foregoing explanation based on the operation of the known laws of osmosis obviously is not complete, for we know that the gland cell has the power to change quickly from a resting to an active state. Evidently there is some mechanism by which the permeability of the membrane at the lumen border of the cell can be changed readily. One school of workers believes that this is a characteristic response of the cell to any stimulus, and endeavors to relate this change to alterations in surface tension brought about by the migration of electrolytes to the border. As evidence for this view, A. B. Macallum cited his demonstration of the migration of potassium to the membrane through which the most active transfer must be taking place. In the cells of the salivary glands, this would be the lumen border; in the epithelium of the small intestine, it would be the end next to the basement membrane.

Another point of view emphasizes the effect of an intracellular splitting of large molecules to yield smaller ones with a resultant increase in osmotic pressure and attraction of water from the blood and lymph into the cell. It has been observed in those cells which contain *zymogen granules*, that the granules near the lumen border become swollen by absorbing water, and become converted into spheres in which salts are dissolved in smaller proportions than exist in the lymph bathing the cells. These swollen structures are then ruptured at the periphery of the cell and discharged into the lumen. This discharge of a fluid containing fewer saline constituents than the cell or surrounding blood plasma brings about increased concentration in the remaining parts of the cell, a process which possibly is assisted by a breaking up of molecules in the protoplasm itself, and which causes an increase in osmotic pressure with a consequent flow of water from the lymph to the cells and therefore from the blood to the lymph. This view is supported by the recent studies by Langstroth and associates[71, 72] of the secretion of protein material by the submaxillary gland following stimulation of the parasympathetic nerve supply. These investigators interpreted their data as indicating that "(a) the mechanism responsible for the secretion of protein material, that responsible for the secretion of water, and that controlling membrane permeability, operate at rates dependent on the rate at which some activating substance is liberated within the gland by the stimulation, and (b) the mechanism responsible for the secretion of protein material consists of a chemical reaction which transforms granule material to a form readily carried out of the cells by the flow of water."

It must be evident that, whatever may be the detailed explanation of the secretory process, it involves work, an expenditure of energy by the secreting cells. Experiments have revealed that during active secretion the pressure within the duct may become even greater than that in the arteries, a condition which could not result if simple filtration were the fundamental and only process. If the cells are able to secrete against a significant pressure, they do work in the process.

CHANGES DURING GLANDULAR ACTIVITY

As in other physiological processes, the secretory activity of cells is associated with a considerable expenditure of energy. The energy changes associated with the resting state are relatively small but nevertheless definite, in contrast to the markedly greater expenditure characteristic of secretory activity. Perhaps the simplest way to study this is to observe the oxygen consumption of the gland. Such observations made on the submaxillary gland of the cat reveal that the change from rest to activity may be associated with as much as a fivefold increase in the consumption of oxygen; furthermore, this increased use of oxygen continues for some time after secretion has stopped, which doubtless means that the energy thus represented is used to build up a new supply of zymogen granules as part of a recovery process. The work of Northup[99] suggests that the creatine phosphate-glycogen mechanism, which operates for the release of energy in muscle contraction, also plays a role in the energy metabolism of the salivary glands.

Secretory activity is also associated with definite changes in electric potential when the active gland is compared with surrounding nonglandular tissue. In this respect, therefore, glands resemble other organs of the body. The studies of Lim, Ivy, and McCarthy[74] on the activity of the gastric glands have shown that one phenomenon common to all secretory activity of the stomach, however induced, is an increased flow of blood through the glands, from which one might be led to suspect that the electric differences are due to these vascular changes. Experiment, however, clearly indicates that this cannot be true, for the electric phenomena occur even when the blood supply is cut off from the gland and as long as the gland continues to secrete under these conditions. Furthermore, it is possible to bring about the vascular changes without concomitant secretion, and under these conditions, the electric changes are not observed; neither is the electric change due to movement of fluid along the duct, because it may be obtained after the duct has been ligated.[20]

The increased vascularity of glands associated with secretory activity would lead one to expect an increase in volume such as occurs, for example, in the kidney. On the contrary, however, it has been shown that the immediate change following a sudden increase of activity, such as can be induced by stimulating the nerve supply, is a decrease in volume. This might be explained as due to the volume of the material stored in the gland cells and then lost in the secretion being greater than the volume representative of the increase in blood and lymph, the net change in volume of the gland therefore being a decrease.

There are drugs which exert opposite effects on glands: atropine paralyzes the secretory process, whereas pilocarpine and acetylcholine promote the flow of secretion. These agents act in such a way as to mimic or block the effects of

nerve impulses in postganglionic parasympathetic secretory nerves and therefore may be used in experiments to determine certain details of the nerve supply to the gland; nicotine blocks conduction across the synapses in autonomic ganglia, and may therefore be used along with the above-named drugs to determine whether certain ganglia are parts of the nervous mechanism involved in the activity of the gland. The ability of atropine to inhibit secretory activity is made use of by the clinician in treating rhinitis and other conditions which are characterized by profuse flow of secretions.

Important observations concerning *the relationship of glandular activity to the blood supply* have been made by experiments in which glands were artificially perfused outside the body. When the submaxillary gland of the dog is perfused with oxygenated Ringer's solution, stimulation of its nerve supply does not produce the usual secretion, but if the Ringer's solution is mixed with blood plasma, the nerve stimulation has its usual effect for a short time. Although no secretion occurs when the oxygenated Ringer's solution is perfused alone, the usual vascular changes still occur in the gland. The results seem to indicate that the presence of some constituent of the blood plasma is essential for the change in the permeability of the cell wall necessary for the process of secretion. Similar results have been obtained during artificial perfusion of the pancreas when secretin was used as the stimulus.

CONTROL OF GLANDULAR ACTIVITY

Having outlined the general nature of the changes occurring in gland cells during their activity, we may now consider the nature of the process by which this glandular activity is controlled. Two mechanisms of control are known: (1) by the nervous system, and (2) by means of chemical agents, the hormones.

Nervous Control

Control through the nervous system is most highly developed—indeed, it may be the only means of control—in glands which are required to produce their secretion promptly, whereas hormone control predominates in those in which prompt changes in secretory activity are not demanded. Thus, nervous control alone is present in the salivary glands, whereas hormone control is predominant in the pancreas, intestinal glands, and in the liver. The gastric glands are partly under nervous control, and partly under hormone control. There are other glands, nondigestive in nature, which are also subject to either nervous or hormone control, according to the promptness with which they are required to secrete. The lacrimal and sweat glands, and the venom glands of reptiles, for example, are practically entirely under nervous control, whereas most of the ductless glands are mainly under the influence of hormones. The exact nature of the nervous control of glandular function has, therefore, been most extensively studied in the salivary glands, and that of the hormonal in the pancreas.

The nerve supply of the salivary glands comes from two sources, the bulbar autonomic (parasympathetic) and the thoracolumbar autonomic (sympathetic). These two innervations do not have the same influence on the secretory activity of the glands and in general they exert opposite effects on the blood vessels

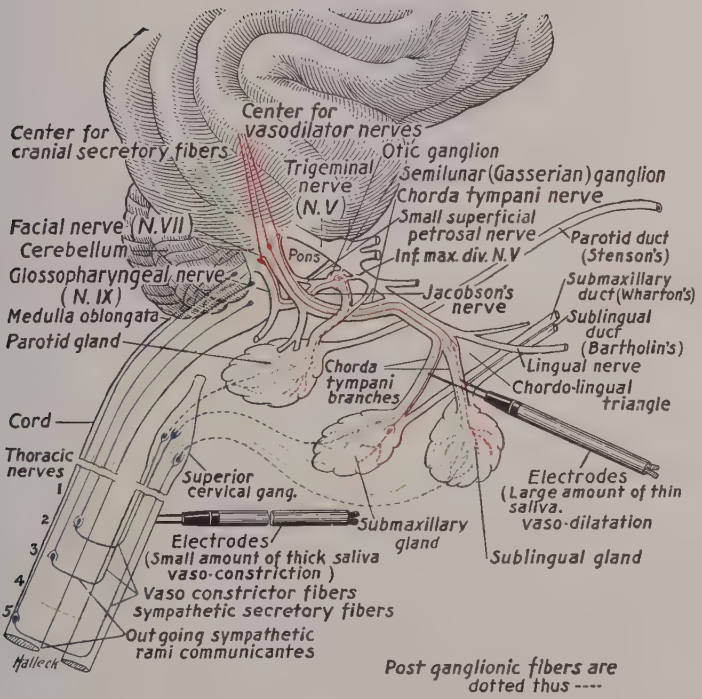


Fig. 324.—Diagrammatic representation of the innervation of the salivary glands in the dog. (After Jackson.)

of the glands; the parasympathetic is vasodilator, the sympathetic vasoconstrictor. In all species of experimental animals a fairly copious flow of secretion can be obtained from any one of the salivary glands by stimulation of its parasympathetic supply. A similar response results from administration of the drug pilocarpine. In the case of the secretory activity of these glands we do not have an example of the rather general rule that when fibers of the two divisions of the autonomic system meet in an effector tissue they exert opposite effects, i.e., excitatory and inhibitory. Stimulation of the sympathetic supply also produces salivary secretion but, "Neither from the submaxillary, the sublingual, nor the parotid gland of any animal does the sympathetic produce a secretion which approaches in amount that which is produced by the cranial nerve." (Langley.) For example, in the dog, faradic stimulation of the sympathetic for a minute produces only two or three drops from the submaxillary gland and even less from the parotid. There are slight species differences; relatively, a little more sympathetic secretion is obtained in the cat and rabbit than in the dog.

On account of their ready accessibility, the submaxillary glands of the dog and cat have been most thoroughly investigated. Here the parasympathetic supply (preganglionic) is represented by fibers of the facial nerve which course in the chorda tympani, and the sympathetic by fibers (postganglionic) that run from the superior cervical ganglion to the gland along its blood vessels (Fig. 324). The parasympathetic postganglionic fibers arise in ganglia which lie mainly in the hilus of the gland, but in part along the distal portions of the chorda tympani. After tying a cannula in Wharton's duct it can be shown that stimulation of the chorda produces an immediate and abundant secretion of rather watery saliva which is accompanied by a marked dilatation of the blood vessels of the gland. It can easily be shown that this secretion is not dependent on the vasodilatation by repeating the experiment after administering a dose of atropine. Stimulation of the nerve then produces vasodilatation but no secretion. Some authorities consider that the atropine acts on the secreting cells in some way, interfering with the secretory process itself; others interpret such observations as due to action of the drug on the endings of the secretory nerves preventing the transfer of excitation to the gland cells, or the chemical changes by which such transfer may be effected. Whatever may be the details of this mechanism, it is clear that one may describe the action of atropine as paralyzing the glands.

The vasodilatation phenomena suggest that the secretion of the gland might be the result of a filtration process; and for this hypothesis to be true, one should always find the secretory pressure within the duct less than the pressure in the capillaries of the gland. Actual experiment reveals, however, that the pressure within the duct may be even greater than that in the arteries, and therefore vasodilatation cannot be responsible for it. This pressure difference is indicative of work done and energy expended by the gland cells in manufacturing and discharging their secretion. For this much oxygen and doubtless other materials are needed, and they are provided in greater abundance by the increase in blood flow. In contrast to these effects, stimulation of the sympathetic nerve supply results in a scanty discharge of a thick viscid secretion concomitant with vasoconstriction.

The production of two such distinct types of secretion, one thin and watery, containing only a small percentage of organic matter, and the other, a thick viscid secretion with a large amount of organic material, has been explained by the hypothesis that there are two kinds of secretory fibers, which Heidenhain called secretory and trophic, the former having to do with the secretion of water and inorganic salts, and the latter with the secretion of organic matter; i.e., with the extrusion of the zymogen granules. This view is supported by the more recent study of Sergeyeva[111] who investigated the effect of various stimuli on the presence and location of zymogen granules in the cells of the pancreas; the results were interpreted as affording "an exceptionally good illustration of the type of nerve effect which Heidenhain designated 'trophic.'" Thus, in the cat the vagus supply to the pancreatic acinous tissue is considered to be purely "trophic" in nature in contrast to the humoral stimulus which elicits a "secretory" effect. Other authorities have suggested that the differences in the secretions resulting from parasympathetic and sympathetic stimulation are due to the different effects of these nerves on the blood vessels of the glands. Although it may not be doubted that vascular changes may influence the quality as well as the quantity of salivary secretion, this explanation can scarcely account for the fact that the dog's submaxillary gland may secrete approximately equal volumes of saliva of quite different content when reflexly excited by the presence in the mouth of two different substances. For example, meat powder provokes a secretion containing about five times as much organic solids as that which is produced by weak acid. It has been found not only that the blood flow through the gland is the same during response to these two substances, but also that the same differences in secretion persist after interruption of the sympathetic supply to the gland (Babkin). In the absence of further evidence it may tentatively be supposed that the chorda tympani contains at least two types of secretory fibers which may be selectively caused to discharge by different reflex stimuli. This would appear to be the case even if it happens that the differences in secretion depend on activation of different sets of gland cells. In considering this problem the reader should bear in mind the all-or-none nature of nerve conduction.

Studies on the salivary glands have yielded evidence in support of the view that impulses in postganglionic autonomic neurons act on the effector cells which they innervate through the agency of *chemical mediators* (see Chapter XI). According to this view, the production of saliva by stimulation of the parasympathetic fibers of the chorda tympani is associated with the peripheral appearance of a substance having the pharmacological properties of acetylcholine; sympathetic stimulation results in production of a substance resembling adrenalin (sympathin). These compounds are presumably produced in the gland and may escape into the blood stream. Dale introduced the words "cholinergic" and "adrenergic" to describe nerve fibers or impulses by reference to the chemical compound involved in the mediation of their effects. The observations of Babkin and associates,[9] constituting an application of this concept to the salivary glands, have been confirmed by several other investigators.[23] The findings of Langstroth and collaborators[72] (see page 890) readily harmonize with this view. The claim of Secker,[110] that these particular humoral agents are even present in the saliva has been challenged by Feldberg and Guimarais,[39] Gibbs,[45] and Larson.[73]

Discussion of the nervous control of secretion would not be complete without some reference to the phenomenon of *paralytic secretion*. It was discovered by Claude Bernard that if the chorda tympani nerve of a dog is cut, there occurs, after about three days, a slow continuous flow of secretion from the gland whose preganglionic parasympathetic innervation had been interrupted. After several weeks the volume of this secretion diminishes until finally the gland has atrophied and no secretion is possible. The continuous flow of saliva occurring under these conditions is called paralytic secretion and may be of some significance in clinical medicine, although its precise cause remains uncertain. When such a phenomenon is observed clinically, some disturbance in the relations of the secretory nerves to the glands in question is suggested, and this should be of interest to neurologists. In dogs exhibiting the disease black tongue, a profuse and apparently uncontrolled flow of saliva is one of the important signs that the animal is in a critical state. Such observations, considered along with the results of experiments in normal animals, support the view already set forth, that the salivary glands must be subject normally to a fairly well-balanced control exercised by the secretory nerves described above, and serious disturbances of this control are only to be encountered in disease.

Hormone Control

This is exhibited best in the case of the pancreas. The crucial experiment demonstrating that this gland is not primarily dependent upon nervous impulses for control of its activity was performed by Bayliss and Starling.[13] Starting with the well-known fact that the application of weak acid to the duodenal mucous membrane excites secretion of pancreatic juice, these workers carefully severed all the nerve connections of a portion of the duodenum, and found on again applying acid to the mucous membrane that the secretion persisted. To explain this result they postulated that the acid must cause some substance to be liberated into the blood stream, which carries it to the pancreas, the cells of which it then excites to activity. To test this hypothesis they scraped off the mucous membrane of the duodenum and ground it in a mortar with weak hydrochloric acid (0.6 per cent). After boiling the mixture so as to coagulate the protein, nearly neutralizing and then filtering, they obtained an extract which immediately caused a copious secretion of pancreatic juice when injected intravenously.

Accompanying the secretion, however, a marked fall in arterial blood pressure was observed, making it possible that the secretion might have been due to a vasodilatation occurring in the pancreatic blood vessels. To eliminate this possibility they prepared an extract that was comparatively free of the depressor substances by extracting intestinal epithelium without any of the submucous tissue. The resulting extract had merely the secretory effect and produced little or no fall in blood pressure. The active substance they named *secretin*. Inasmuch as the extracts prepared with water or salt solution contained the depressor substances but had no effect on the pancreas, they suggested that there is an inactive precursor substance, prosecretin, in the intestinal mucosa, which is activated by acids.

For many years the specific nature of secretin was challenged, particularly by Popielski, who attributed the secretory effect of tissue extracts to vasodilatin present in them. The original thesis of Bayliss and Starling received further support, however, by the discovery that vasodilatins are more soluble in alcohol than secretin; by utilizing this fact, it is possible to secure preparations which have a powerful secretory action on the pancreas when injected intravenously, but no effect on blood pressure. Mellanby[89] in 1926 succeeded in devising a method for making a very potent preparation by extracting the duodenal mucosa with absolute alcohol and then precipitating the secretin with acid, dissolving the precipitate in alcohol and reprecipitating by means of acetone. Luckhardt, Barlow and Weaver[78] made a great advance when they discovered that simple acid extraction of the intestinal mucosa—made by filling the first five feet of the intestine with the acid and allowing this to extract for thirty minutes, then neutralizing and filtering—yielded a preparation potent as a secretin but devoid of depressor substance. The necessity of attempting separation of the two factors was thus avoided at the outset. Other secretin preparations have been made by Still[112] and by Ivy and associates.[63] Secretin was finally obtained in crystalline form by Agren,[1] who made an extensive study of its physiological and chemical properties.

The secretin theory as put forth by Bayliss and Starling postulated secretin as a chemical agent elaborated in the cells of the intestinal mucosa by contact

of those cells with acids, and passing by way of the blood stream to the pancreas where it exerted its stimulating action. The isolation of secretin in crystalline form constitutes powerful support for the theory, but a critic would be justified in claiming that this means merely the isolation of a particular pharmacologic agent which can act upon the pancreas; that proof of the hormone mechanism must involve physiologic experimentation in animals. Such proof has been obtained. For example, cross-circulation experiments have been performed in which the circulations of two animals are joined and acid placed in the intestine of one of the animals, with the result that the pancreas in each animal responds by secreting juice. The work of Ivy and associates[37] has finally given us the best kind of proof desired. In their first experiments the tail of the pancreas of the dog was transplanted under the skin, thus bringing the duct to the surface to yield a fistula. Later, after new blood vessels had developed for the transplant, the original blood and nerve supply was severed. It was found that food or hydrochloric acid given by mouth provoked a characteristic secretion. These experiments were open to the criticism that food products absorbed from the intestine might have been responsible. Therefore, in later studies,[61] both jejunal and pancreatic transplants were prepared in the same dog. When hydrochloric acid was placed in the transplanted jejunum, juice was secreted by the transplanted pancreas. Suitable control materials placed in the jejunum were without effect.

The suggestion of the existence of prosecretin, a precursor of the active hormone, has not been so successfully substantiated. As Still points out in his review of literature on this problem, "the views of most workers . . . rested upon suggestive rather than conclusive data."

According to Agren[1] who used a crystalline preparation of secretin for his studies, the hormone contains about 0.68 per cent sulfur, which corresponds well to the theoretical 0.64 per cent, if the molecule contains 1 atom of sulfur and has a molecular weight of about 5,000. It contains much arginine (6.60 per cent) and histidine (3.96 per cent), some lysine, but apparently no cystine, tyrosine, or tryptophane. It behaves as a basic substance, gives some but not all of the tests for protein, and is digested by proteinases, all of which suggests that it is fundamentally protein in nature. It may be inactivated by treatment with 0.1 N sodium hydroxide, and this loss of activity is associated with the appearance of the ninhydrin reaction, suggesting that the inactivation is due to a splitting of a peptide linkage without further disruption of the molecule. The activity cannot be related to the presence of free amino groups. With respect to physiological properties, Agren's preparation was found on intravenous injection to produce secretion of the pancreas, liver and intestinal glands, an action which may be described as a "generalized intestinal diuretic" effect. It had no influence on the internal secretion of the pancreas, or on the concentration of either blood sugar or blood amylase, three effects which had been cited by earlier workers as due to secretin; in the earlier work these changes were due to other substances present in the crude extracts which were used. Pure secretin-HCl, unlike impure preparation, produces no lowering of blood pressure, no effect on the gallbladder or on isolated segments of intestinal muscle of the rabbit.

Any acid when applied to the intestinal mucous membrane is capable of liberating secretin, and so are certain other substances, such as mustard oil.

Secretin is not effective if placed in the intestinal lumen. This may be related to the ease with which it is destroyed by such digestive enzymes as those present in the pancreatic, gastric, and intestinal juices.

The pancreatic juice produced by the injection of secretin, like that elaborated under normal conditions, does not contain any active trypsin, but instead contains its precursor, trypsinogen. This becomes converted into trypsin in the intestine, being activated by mixing with enterokinase, an enzyme present in the intestinal juice. It has been suggested that this mechanism protects the mucosa of the pancreatic duct against autodigestion by trypsin but this explanation is not entirely satisfactory.

There is a nervous control of pancreatic secretion as well as that mediated through secretin. Prior to the discovery of secretin, Pavlov and his pupils had published numerous experiments to show that the secretion of pancreatic juice may be evoked by stimulation of the vagus nerve. The amount of secretion produced by nervous stimulation was, however, never as large as that subsequently found to be produced by secretin, and for several years after the discovery of this hormone, doubt existed as to the correctness of Pavlov's claim. As in many other fields of physiological science, investigators attempted to show that one or the other mechanism operated exclusively, and they were not inclined to consider the possibility that both might exist side by side. This period might also be considered as representing essentially an experimental study of the extent and limitations of the newly discovered hormone mechanism. There is little doubt, however, that the vagus nerve carries secretory fibers to the pancreas, and stimulation of them results in a flow of pancreatic juice which, besides being less copious than that following secretin injection, differs from it in the important fact that it contains not trypsinogen but active trypsin. Since normal pancreatic juice contains chiefly trypsinogen, and only a small amount of trypsin, it may be argued that the vagus control of the normal secretion cannot be as important as that mediated by the hormone secretin. The vagus secretion of pancreatic juice is, moreover, paralyzed by atropine, which has no action on the secretin mechanism.

The copious secretion of pancreatic juice produced by secretin, on the one hand, and the scanty, thick secretion evoked by vagus stimulation, on the other, call to mind similar differences observed in the secretion of saliva as the result of chorda-tympani or sympathetic stimulation. It will be recalled that from these results the conclusion was reached that there must be secretory and trophic fibers concerned in the control of the activities of gland cells. Interesting corroboration of this conclusion has been obtained by *histological examination of the pancreas following secretin or vagus activity.* After the repeated injection of secretin, it is difficult to observe any signs of fatigue in the cells; the zymogen granules remain practically as numerous as in a resting gland, but in the clear protoplasm of the outer third of the cell, it is said that fine channels can be seen. Through these channels water is believed to pass from the blood toward the lumen and in its course to carry with it some of the zymogen granules without, however, changing them. Thus, when the gland cells are stained with eosin and orange, after secretin activity some of the zymogen granules can occasionally be seen in the lumen of the acini stained with eosin like those in the cell itself.

After vagus stimulation the appearances are different; not only are the granules more decidedly removed from the cells, but they undergo a preliminary change; they lose the property of staining with eosin and become stained with orange, at the same time increasing in size so as to form vacuoles. These vacuoles may wander into the ductules, and when they are present here they are stained by orange (Figs. 323 and 325) (Babkin et al.[10]).

Why there should be both a nervous and a hormone control of the pancreatic secretion is not clear. The ideas of Langstroth and his associates[71, 72] representing essentially a combination of the Heidenhain concept of "trophic" and "secretory" stimuli and the Dale idea of "cholinergic" and "adrenergic" mediation of nervous impulses through specific chemical compounds, constitute an interesting recent approach to an answer to this question which takes account of the secretion of both water and electrolytes as well as organic complexes. In the case of the pancreas the nervous influences through both the vagus[111] and the splanchnics[8] appear to be quite definitely related to the discharge of large molecules of organic material and movement of granules, and similar to Heidenhain's "trophic" influence. Also, the hormone secretin produces primarily, although not exclusively,[68] a flow of water and electrolytes, which is a phenomenon comparable to what Heidenhain called a "secretory" response. However, the fact that secretin does to some extent stimulate enzyme production[68] makes it clear that the above statements constitute an oversimplification of the problem and do not afford a complete explanation.

The flow of pancreatic juice is important when there is food material in the small intestine, and this material would normally appear as part of a discharge of stomach contents. One can then understand the value of the secretin mechanism operating in response to the presence of the acid gastric discharge; such an arrangement would insure the proper sequence of pancreatic juice flow after gastric digestion has taken place. The pancreatic juice secreted in response to secretin contains much water and inorganic salts, chiefly bicarbonates, whereas stimulation of the vagus excites the secretion of enzymes as part of a more viscous juice. Mellanby[89] has suggested that the prime function of the juice evoked by the secretin mechanism may not be to provide enzymes but rather alkali with which to neutralize the acid discharged through the pylorus. This idea receives considerable support when one considers the results of studies of experimental duodenal ulcer. The technique found most effective by Mann and others[83] in the production of these ulcers consists in operating on animals in such a way as to divert the alkaline secretions of the pancreas and liver from that part of the small intestine which receives the acid discharge from the stomach; in this part of the intestine, unprotected (?) by the alkaline pancreatic juice and bile, ulcers appear with great regularity.

The rôle of the vagus mechanism may be similar to that of the sympathetic fibers to the salivary glands: nervous impulses coming over these fibers affect in some way the intracellular processes involved in the elaboration of the complicated enzyme molecules. There is another point of view that may be taken. When considering any digestive process that requires activation of a precursor substance or the maintenance of special conditions of acidity, or alkalinity, etc., quantitative examination of the different variables suggests that it may be relatively more important to secrete an abundance of material (alkali, or acid) needed

for securing the optimal conditions of enzymic activity (trypsin or pepsin) than to vary the amount of the enzyme secreted. It is an interesting fact that the salivary glands, the pancreas, and the stomach all give evidence of two types of processes involved in secretion, one having to do with the elaboration of special organic material peculiar to the secretion, the other, with the flow of water and electrolyte, perhaps a flushing action, through the cell. In the salivary glands, both of these processes seem to be subject to nervous control; in the pancreas, only one is under nervous control, the other being influenced by the hormone

Fig. 325.—Pancreatic acini and stained with hematoxylin. The acini at the top and to the left of the figure are from a resting gland, those to the right being from one that had been secreting for over three hours as a result of acid in the duodenum. The lowermost figure is from a gland, the vagus nerve supply of which had been stimulated off and on for several hours. Note that the zymogen granules are extruded only after vagus activity, not after secretin activity. (From Babkin, Rubaschkin and Ssawitsch.[19])

mechanism with alkali salts as the electrolytes of greatest value; in the stomach, the situation is more complicated, yet there is definite evidence that both nervous and humoral mechanisms play a rôle, the latter being concerned in the elaboration of a highly fluid secretion with hydrochloric acid as the important electrolyte; this possible rôle of the acid secretion of the parietal cells of the gastric mucosa in flushing the tubular glands and thus washing out their thick pepsin or

pepsinogen-rich product of chief cell activity, is illustrated in the experiments of Gilman and Cowgill,[47] which will be discussed in more detail when we come to consider gastric digestion.

As was emphasized before, when discussing the dual nervous control of salivary secretion, it is reasonable to believe that the two types of gland control, nervous and hormonal, operate together to secure a balanced control which is capable of some normal degree of variation to meet special situations; and that it is possible for one or the other of the extreme conditions, represented by failure of either control mechanism to operate in appreciable degree, to occur either as the cause or the result of disease. As an illustration of this last point, we may cite the observation of Ivy et al.,[38] that pancreatic dysfunction (failure to provide proper alkali [?]) may be associated with hypersecretion of gastric juice.

CHAPTER LXI

PHYSIOLOGY OF THE DIGESTIVE GLANDS

In the preceding chapter the fundamental phenomena characteristic of the secretory process were described. The cells endowed with the property of elaborating digestive secretions are found gathered together in many organs forming parts of the alimentary tract. No one gland serves all of the digestive needs of the body; each cooperates, as it were, with the other glands. As food passes through the alimentary tract, the different secretions are called forth in appropriate order, and each performs the specific rôle assigned to it, with the result that all foods requiring digestion have been duly subjected to this process and the products given ample opportunity for absorption by the time the swallowed food has passed through the ileocecal valve into the large intestine. The conditions under which each gland elaborates and discharges its secretion, being numerous and varied and correlated with the activities of other organs, must be studied if the student of physiology and medicine is to understand the basis of certain diseases of the alimentary tract.

THE SECRETION OF SALIVA

Methods of Study

A simple method for studying the mechanism of salivary secretion consists in isolating a salivary duct in an anesthetized animal, tying in it a cannula, and observing the flow of saliva under various conditions. It was by means of such a technique that the fundamental observations concerning the rôle of certain nerves, drugs and hormones were made. It is clear, however, that the conditions of such experiments are far from ideal, because they tell us nothing about the possible responses of the salivary glands to stimuli operating in a conscious normal organism. Pavlov succeeded in devising a permanent salivary fistula thus meeting the chief criticism of the older technique. The mucous membrane surrounding the opening of the duct is cut to form a small disk of tissue at the center of which is the duct opening. The duct is freed a short distance by careful dissection, and the disk then passed through a wound in the cheek to the outside where it is sewed to the edges of the skin wound. Healing takes place without the formation in the duct of any stricture due to scar tissue. After the wound has healed, the secretion can readily be collected in a receiver over the duct fistula, the animal being in every other way in a perfectly normal condition. By using a graduated receiver of glass, the experimenter can readily observe and measure in a wide-awake, sensitive animal, the saliva secreted in response to various experimental conditions. The fistula can be made with the duct of the submaxillary gland, in which case the secretion is from a mucous gland; if the duct from the parotid is employed, the secretion is from a serous gland. In preparing a permanent salivary fistula of the Pavlov type, the dog has been found to be especially valuable.

Factors Causing Secretion of Saliva

Inasmuch as the salivary glands are entirely under nervous control, this may be made the basis for a simple classification of the types of secretory responses. When secretion occurs, it is caused by impulses acting on a nerve center or centers in the medulla oblongata, the exact location of which for the different glands has been worked out by Miller.[93] The impulses acting on these centers

may be transmitted along afferent nerves coming from the mucous membrane of the mouth, nares, etc., or they may come from the higher centers over pathways within the brain.

Unconditioned Responses.—Secretion may be obtained by a simple reflex mechanism, through stimulation of various receptors located in the mouth. This reflex is remarkably prompt when an irritating substance is placed in the mouth, the copious secretion acting to dilute the irritant and to aid in its removal. There is some degree of adaptation of the secretion to the physical state of the material. If the dog is given meat, there is a secretion of thick viscous saliva chiefly from the submaxillary gland; if, on the other hand, the meat is dried and pulverized, the secretion which it calls forth will be very copious and watery, the product of parotid gland activity. The mucous secretion called forth by meat will serve to lubricate the bolus of food and thus facilitate its swallowing, whereas the thin watery secretion produced by the dry powder will have the effect of washing the powder from the mouth. Although mechanical stimulation of the mucosa seems to be quite effective in some instances, there are situations in which it does not seem to be adequate. For example, the presence of pebbles in the mouth calls forth but little secretion whereas with sand, secretion immediately becomes copious. Chemical stimuli are also effective. Thus, weak acid causes a copious secretion, while weak alkali has no effect; disagreeable, nauseous substances also excite secretion. The above differences in the response of the glands according to the mechanical condition of the food have been observed in the case of the parotid gland, increase in the submaxillary secretion being obtained only when foods are actually placed in the mouth. It is evident that, with at least two different types of glands able to function, a considerable range of variation is possible with respect to the properties of the mixed secretion finally discharged.

Conditioned Responses.—The investigations that have been made on the conditions of psychic secretion of saliva are still more interesting and important. Their importance depends not so much on the information they give us concerning the secretion of saliva as such, as on the methods they afford us for investigating the various conditions that affect the psychic processes associated with the taking of food. It is from the psychic rather than from the physiologic standpoint, therefore, that these observations are of importance, for they permit us, by objective methods, to study on dumb animals problems that would otherwise be beyond our powers of investigation. Many of the results, with their bearing on the functions of the higher nerve centers, have been discussed elsewhere (Chapter XX). Meanwhile, however, even at the risk of repetition, it may not be out of place to cite a few of the most interesting experiments.

If a hungry animal is teased with a food for which he has a great appetite, a copious secretion of saliva immediately occurs. If the teasing is continued without giving him the food, and the procedure repeated on several succeeding days, it will be found that he responds less and less to the teasing by salivation. Evidently, therefore, the reflex is conditioned by the animal's receiving the food. The dog may be conditioned to secrete saliva in response to the sound of a particular tuning fork by the simple procedure of always sounding the fork just before the food is given; eventually the animal responds to the sound of the fork although no food is given.

It is possible to condition the dog to secrete saliva in response to the smell and sight of a food for which the animal has no appetite. To do this, we repeatedly offer first of all the unappetizing food, followed, after a time, by presentation of the appetizing food. Eventually the animal secretes saliva when the unappetizing morsel is offered. He has learned to associate the presentation of the unappetizing food with the subsequent gratification of his appetite. The experiment can even be performed so that a definite interval of time elapses between the application of the stimulus and the salivation: if the animal is teased on successive days with food for which he has an appetite but is not given the food until after ten or twenty minutes, presentation of this food will come to be followed by salivation—not immediately, but after the exact interval of time that had been allowed to intervene in the training process. During this interval there must be an inhibition of psychic stimulation of the salivary centers by other nerve centers. It is of great interest that this inhibition may itself be inhibited by various forms of stimulation of the nervous system (see page 233).

THE SECRETION OF GASTRIC JUICE

Methods of Investigation

Unlike the salivary glands, which are provided with ducts, the stomach is essentially a bag, the entire lining of which contains glands whose secretion is eventually discharged into the intestine; this bag is also able to receive swallowed material which may be both food and saliva. The problem of securing pure gastric juice for study is therefore a much more difficult one to solve. One of the most interesting chapters in the history of physiology concerns the methods which from time to time have been evolved for the collection of this juice and for studying the digestive processes in the stomach.

The earlier investigators concerned themselves with tests of the various ideas of gastric function which had been suggested. Hippocrates, who has been called the Father of Medicine, took as his illustration of the digestion which occurs in the stomach the solution of foods which results from cooking; heat coction was considered to be the fundamental process. It was realized that the living organism is capable of producing heat, and this idea was combined with the other, resulting in the hypothesis that the stomach is the locus of heat production and gastric digestion is essentially a solution of food by heat. The Belgian philosopher, Van Helmont (1577-1644) likened digestion to the fermentation processes in nature; Sylvius (1614-1672) taught his medical students in Leiden that gastric digestion is a fermentation. The French philosopher and mathematician Descartes (1596-1650), and the English anatomist Willis (1621-1675), used the observations of physicians that acid material is present in vomitus as the basis for the suggestion that gastric digestion is brought about through the elaboration of some powerful acid similar to nitric or phosphoric acid, the most potent acids then known. Borelli (1608-1679), the Italian engineer, who brought his talents to bear on problems of physiology, likened the stomach to the crop of the bird, and suggested that the chief function of the stomach is to grind the food. The first really experimental attack on the problem was made by the great French scientist Réaumur (1683-1757), who performed numerous experiments on a pet kite, able to regurgitate the bones of its prey. Hollow spheres and similar objects with perforated walls which could resist crushing, were filled with different kinds of foods and then given to the bird. After having been regurgitated, these were examined. It was found that meat had dissolved whereas cereal grains and certain other foods were practically unaffected. Sponges were also placed in these special containers, and when regurgitated, were squeezed dry of the gastric juice which they had absorbed. This work was followed by that of the Italian Abbé Spallanzani (1729-1799) who employed similar methods, notably the use of small

perforated wooden tubes containing foodstuffs and covered by small linen bags. After the bags were passed through the rectum, he found that considerable erosion or digestion of the food had occurred, but that the wooden tubes, however thin-walled they might be, were not crushed. In order to secure samples of the gastric juice free from food, these earlier investigators resorted to the technique of swallowing sponges attached to threads, which after being in the stomach for some time were withdrawn and squeezed dry of juice. The last sentence in Spallanzani's treatise, "the gastric juice is antiseptic," is a famous one because of the extent to which it has been confirmed in later researches.

The next great contribution came from the United States. Dr. Beaumont, a surgeon in the service of American troops located at Mackinaw in northern Michigan, reported in 1833, his observations made on a Canadian voyageur by the name of Alexis St. Martin, who by the premature discharge of his gun had wounded himself in the stomach. The wound, which never completely healed, left a permanent gastric fistula. Beaumont found it possible to see through this fistula the interior of a normal living stomach. This opportunity was capitalized by arrangements to keep Alexis St. Martin in Dr. Beaumont's service for several years, during which time numerous observations were made on the process of digestion in the stomach—observations many of which are of great value even at the present day. Many of the statements found in textbooks concerning the relative digestibility of common foods in the stomach are based upon the reports of Dr. Beaumont.

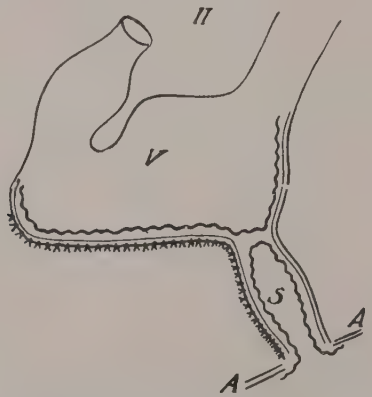


Fig. 326.—Diagram of stomach showing miniature stomach (*S*) separated from the main stomach (*V*) by a double layer of mucous membrane. *A.A.*, is the opening of the pouch on the abdominal wall. (Pavlov.)

The publication of Beaumont's observations soon stimulated physiologists to make similar fistulas in animals. It is evident, however, that even a simple fistula of the Alexis St. Martin type cannot yield pure gastric juice uncontaminated by swallowed saliva or material regurgitated from the intestine. Heidenhain attempted to solve this problem by cutting the stomach in such a way as to make two separate pouches, one retaining its connections with the esophagus and intestine, the other draining through an opening in the abdominal wall. The results of Heidenhain's experiments are, however, open to the objection that the secretion of the isolated pouch may not really correspond to that occurring in the main stomach, since the connections of the isolated pouch with the central nervous system must have been severed. His pupil, the Russian physiologist, Pavlov, devised an ingenious improvement on his operation in which the pouch or "miniature stomach" remains connected with the main stomach through a considerable width of mucous and submucous tissue and in which the nervous connections are not severed. The essential nature of this operation will be evident from the accompanying diagram (Fig. 326).

More recent observations have been made by Cannon, Carlson and Ivy. Cannon fed animals food impregnated with bismuth subnitrate, and then exposed the animal to the x-rays. A

shadow is produced by the food mass in the stomach, and from the changes in the outline of this shadow facts have been collected, not only concerning the movements of the viscus, but also concerning the rate of discharge of food into the intestine and therefore the duration of the gastric digestive process. Carlson's contribution has been rendered possible by his good fortune in having in his service a second Alexis St. Martin (called "Mr. V" in the literature), a man with complete closure of the esophagus and a gastric fistula large enough to permit of direct inspection of the interior of the stomach. Ivy has utilized the techniques of modern surgery to prepare in dogs the Pavlov or Heidenhain pouch combined with isolated loops of the intestine or other operations of value in elucidating the fundamental mechanisms involved in gastric secretion.

The Cephalic Phase of Gastric Digestion

The first stimulus to the secretion of gastric juice is nervous in origin, involves the brain, and is dependent on the stimulation of various receptors located in the head. The earlier investigators attributed this to the gratification of the appetite and the pleasure of taking food. Following suggestions made by certain observations in the clinic, Pavlov was the first thoroughly to investigate this problem. For this work he used dogs provided with the "miniature stomach" and an esophageal fistula. When food was given by mouth to these animals, it was chewed and swallowed in the usual manner, but before reaching the stomach, it escaped through the esophageal fistula. This experiment is known as "sham feeding." Within a few minutes after giving food the gastric juice was found to be secreted actively and if the feeding process was continued, which could be done almost indefinitely since the animal never became satisfied, the secretion continued to flow. Thus, in one instance Pavlov succeeded in collecting about 700 ml. of gastric juice after sham feeding an animal for five or six hours in the manner above described. The presence of food in the mouth is undoubtedly the most effective stimulus of this flow of so-called psychic juice. The stomach of Carlson's patient would not secrete in response to the mere thought of food, but was stimulated when food was actually present in the mouth. Pavlov considered that the secretion obtained under these conditions was definitely associated with activity of the higher centers in the brain, and therefore should be called a "psychic secretion."

The sham feeding causes stimulation of the gastric secretion through impulses transmitted to the stomach along the vagus nerves; for it has been found, in animals in which the vagus nerve has been cut, that the sham feeding no longer induces a secretion of gastric juice. The question therefore arises as to how the nerve center is stimulated. Three possible causes may be considered: (1) mechanical stimulation of the sensory nerves of the mouth; (2) chemical stimulation of these nerves; (3) the agreeable stimulation of the taste buds and olfactory endings concerned in the tasting of food. In investigating these possibilities, mechanical stimulation was readily ruled out by showing that mere taking of solid matter in the mouth did not excite any secretion, although it might cause a flow of saliva. Mere chemical stimulation could not be the cause, for no secretion was induced by placing substances such as acetic acid or mustard oil in the mouth. By exclusion, then, it would appear that the adequate stimulus must consist in the agreeable stimulation of the taste buds, etc. This would constitute support for Pavlov's idea that there is a psychic factor involved.

Further justification for this conclusion was readily secured by noting that foodstuffs for which the animal had no particular desire or appetite failed to excite the secretion. Most dogs, for example, although they may take it, are not particularly fond of bread, and when fed with it, these animals do not produce any appetite juice. In one animal that showed considerable liking for bread, active secretion occurred when he was fed with this foodstuff.

Pavlov further noted that usually it was not necessary actually to allow the animal to take the food into his mouth, but that mere teasing with savory food was sufficient to cause the secretion, and that in highly sensitive animals even the noises or other events usually associated with feeding time were sufficient to excite it. In the case of a hungry animal, the mere approach of the attendant with food, or some other noise or action definitely associated with feeding time, was a sufficient excitant. The appetite juice when started was found to persist for some time after the stimulus causing it had been removed.

Carlson succeeded in confirming most of these observations in man. He noted, however, that the secretion produced by seeing or smelling or thinking

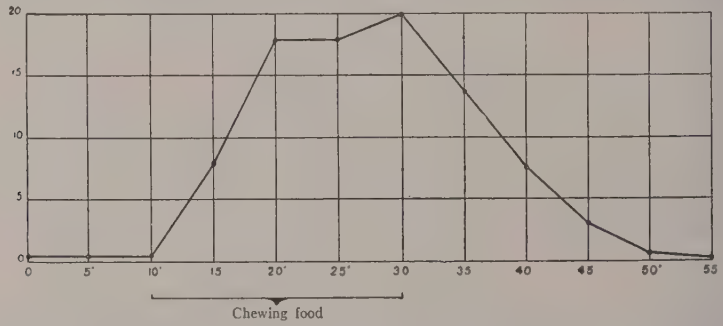


Fig. 327.—Typical curve of secretion of gastric juice collected at 5-minute intervals on mastication of palatable food for 20 minutes. The rise in secretion during the last 5 minutes of mastication is due to chewing the dessert (fruit) for which the person had great relish. (From Carlson.)

of food is much less than would be expected from Pavlov's observations on dogs. Even when his subject was hungry, Carlson did not observe that the bringing of a tray of savory food into the room caused any secretion of gastric juice. It is, of course, to be expected that the quantity of the psychic secretion will not be the same in different individuals. It has been observed by Pavlov, for example, to vary considerably in the case of dogs, and it is very likely that it will vary still more in man, with his more highly complicated nervous system. In no case could Carlson observe any secretion of gastric juice to be produced by having his patient chew on indifferent substances, or by stimulating the nerve endings in the mouth by substances other than those directly related to food.

In man the rate of secretion is proportional to palatability of the food, the smallest amount, during twenty minutes' mastication of palatable food, being 30 ml. and the largest 150 ml., in a series of 156 observations. A typical curve showing the amount of the secretion is given in Fig. 327. To construct this curve the gastric juice was collected during five-minute intervals while the man was chewing a meal of average composition and of his own choice. An interesting feature is that the secretion rate was highest in the last five-minute period,

this being the time during which the dessert was being taken, for which this man had a great relish. Quite clearly there was a direct relation between the rate of the secretion of the appetite juice and the palatability of the food. It will further be observed that it took only from fifteen to twenty minutes after discontinuing the chewing before the rate of secretion of juice returned to its original level.

The practical application of these facts in connection with the hygiene of diet and the feeding of patients during convalescence is obviously very great. However perfect in other regards a diet may be, it will probably fail to be digested at the proper rate unless it is taken with relish. Frequent feeding with favorite morsels is more likely to be followed by thorough digestion and assimilation than occasional stuffing with larger amounts. We see in these experiments an explanation of the well-established practice of starting a meal with something savory. An *hors d'oeuvre* is nothing more than a physiological stimulant to appetite. It is also interesting from a practical standpoint to observe that with those who have a keen relish for sweetmeats the taking of dessert has a real physiological significance, for, as in Carlson's patient, it stimulates toward the end of the meal a further secretion of the gastric juice, and thus insures a more rapid digestion of the food. Good cooking, it should be remembered, is really the first stage in digestion, and it is the only stage over which we can exercise voluntary control. Addition of water to the food within certain limits increases the secretion of gastric juice, and weak alcohol (0.5-10 per cent) is still more effective. Iced water and strong alcoholic drinks act as inhibitory agents.

There can be little doubt that in the normal individual this excitation of the gastric secretory process by the stimulation of receptors in the mouth, eyes, etc., without the actual presence of food in the stomach, is associated with the stimulation of certain cortical cells in the brain, and to this extent, therefore, justifies the use of the term *psychic secretion* in this connection. Zeliony,[127] however, has been able to show that the fundamental nervous mechanism can operate without concomitant stimulation of the cerebral cortex. Sham feeding of a decorticate dog resulted in secretion of gastric juice when the animal tasted food. From this it is evident that other than solely cortical responses are concerned. Because of this, Ivy[60] has suggested that the initial phase of gastric secretion be termed the *cephalic phase,* denoting that it is due to stimuli acting on sensory end-organs located in the head. Under this heading two types of responses may be distinguished: (1) those passing through the cerebral cortex (psychic), and (2) those involving the thalamus, midbrain or medulla, the afferent sensations being caused by the sight, smell and taste of food, chewing and swallowing quite probably playing the rôle of decreasing the threshold of the reflex arcs involved. The vagi are the efferent nerves concerned in conducting the impulses from the gastric secretory center or centers to the gastric glands.

The Gastric Phase of Gastric Secretion

When food is present in the stomach the gastric glands are stimulated to secrete. Pavlov investigated this phenomenon in dogs provided not only with a miniature stomach but with a simple fistula of the main stomach as well. The behavior of the secretion of gastric juice as a whole could be followed by collecting that which was secreted in the miniature stomach, for it was shown in control experiments, that this secretion runs strictly parallel with that in the main

stomach, being quantitatively a definite fraction of it—according to the size of the miniature stomach—and qualitatively identical. The miniature stomach, in other words, mirrors the events of secretion in the main stomach.

Local Mechanical Stimulation.—It was observed that when the animal was allowed to take the food into the main stomach by the mouth and esophagus, the secretion from the miniature stomach continued to flow until the process of gastric digestion had been completed, a result which was quite different from that obtained after sham feeding. The only possible explanation for this result is that the food in the stomach sets up secretion as a result of local stimulation. To investigate the nature of this local stimulation, whether mechanical or chemical, food and other substances were placed in the main stomach through the gastric fistula without the animal's knowledge, so as to avoid possible psychic stimulation, and the secretion observed from the miniature stomach. In these experiments of Pavlov, mechanical stimulation of the gastric mucosa by placing inert objects, such as a piece of sponge or sand in the stomach, were without effect; Pavlov therefore claimed that mere contact of the food with the gastric mucosa does not constitute an effective stimulus for gastric secretion. Beaumont had reported that rubbing the gastric mucosa of Alexis St. Martin's stomach resulted in the appearance of droplets of fluid on the surface of the stomach wall, presumably, in the light of our modern knowledge, at the points where each lumen of a tubular gland joined the lumen of the stomach cavity proper. Pavlov explained these observations of Beaumont as due to psychic secretion by some psychic stimulus received by Alexis St. Martin. It remained for Ivy and associates[60, 74] to demonstrate in a dog with an isolated stomach—where the esophagus was joined to the intestine, and the isolated stomach provided with a fistulous opening through the body wall—that mere contact alone of the mucosa with an inert object is not sufficient, but that if, at the same time there is a certain degree of stretching of the stomach wall associated with expansion of the viscus to accommodate the mass, the stimulus is an effective one. The experiments of Ivy in this connection constitute a closer approximation to the conditions which prevail in the normal organism. The student should realize that the empty stomach is not like a large empty bag, but rather a contracted viscus with the walls more or less in contact with each other; when swallowed food enters the stomach, the organ expands sufficiently to accommodate it and maintains a moderate tonic contraction on the contents, this pressure being altered at intervals as a result of the peristaltic waves which occur from time to time. This contact-plus-distention stimulus is effective in promoting the flow of gastric juice to aid in digestion of the mass.

The mechanical stimulus has been demonstrated to be effective not only in the pouch consisting of the isolated entire stomach, but in separate pouches consisting of the pyloric and the fundic portions. Curiously enough, distention of the pyloric pouch will stimulate secretion in the fundus. Mechanical stimuli are not effective if atropine has been given; they are also inhibited by the introduction of fats into the intestine (see "Gastric Chalone" below).

Local Chemical Stimulation.—It has been found that various foods show considerable difference in the degree to which they can promote the flow of juice. Water and egg white have only a slight effect; bread and starch in a dry state do not stimulate. On the other hand, when protein that has been partly

digested by means of pepsin and hydrochloric acid is introduced into the stomach, there is an immediate flow of secretion. A solution of commercial peptone has been found to be effective, which confirms the observations just cited. Evidently, certain foods, which in the swallowed state are ineffective, are first digested by the juice called forth in response to the so-called psychic stimuli, after which the products of this digestion further stimulate the secretory process. In this connection should be mentioned Pavlov's observation that commercial beef extract is effective in promoting the flow of gastric juice. This is an interesting finding, because previous studies of the nutritive value of this material—utilization of its nitrogen, etc.,—had led to the conclusion that it is valueless as a food. The discovery that this substance can promote the flow of gastric juice gives it a physiological use which may be desirable in certain individuals. This effect of meat extract is interesting also in connection with the practice of taking soup as a first or early stage of dining. It not only excites the flow of appetite juice but also serves as a direct stimulus of the gastric glands as soon as it reaches the stomach.

Pavlov attempted to evaluate for gastric digestion the psychic phase with and without the gastric phase. He placed weighed quantities of meat attached to threads in the stomach through a gastric fistula, and after some time removed them and determined by the difference in weights the extent to which digestion had occurred. It was found that when the appetite juice was excited by sham feeding at the same time that food was placed directly in the stomach, its digestion was much more rapid than in cases in which it was placed in the stomach without the animal's knowledge, as when he was asleep.

The nature of the mechanism by which the purely gastric phase of secretion takes place has received much attention by investigators. Popielski showed that this secretion still occurs after all the nerves proceeding to the stomach are cut, and concluded that the secretion must depend on a local reflex mediated through the nerve structures present in the walls of the stomach itself. Edkins[36] proposed a hormone mechanism substantially as follows: contact of acid and food substances with the mucosa of the pyloric portion of the stomach causes the elaboration and absorption into the blood of a hormone called gastrin which is carried to the glands of the fundus and excites them to activity. The chief facts that may be cited against this theory are (1) that a gastric secretin can be isolated from many animal as well as plant tissues, and therefore the gastrin of Edkins is not specific as to location in the pyloric mucosa, and probably not as to action or kind (Ivy), and (2) that attempts to demonstrate this hormone in the blood have met with failures or unsatisfactory results. Using a pouch of the entire stomach, Ivy and associates found that "meat or meat juice is the only one of the common food substances as yet used that stimulates gastric secretion when applied in amounts insufficient to involve stimulation by distention. Histamine and β-alanine are pure chemical substances that stimulate on local gastric application." In view of the fact that the intestinal phase of gastric secretion (see below) unquestionably involves a hormonal mechanism, one cannot say dogmatically, that such a mechanism is not involved in the purely gastric phase of secretion. It does appear proper to state, however, that the gastrin theory as enunciated by Edkins is inadequate. MacIntosh[80] has summarized considerable indirect evidence suggesting that histamine may be a step in the production of gastric juice when the vagus is stimulated. Sacks and col-

laborators[109] isolated histamine from the pyloric mucosa, and concluded that "histamine is the gastric hormone, or if not, there is no gastric hormone, or the gastric hormone has never been extracted from pyloric mucosa." More recently, however, Komarov[67] has reported the extraction from the pyloric mucosa of a protein-like substance having a specific secretagogue effect on the fundic glands. Komarov interpreted his observations as supporting the "gastrin" theory, and also suggested that "gastrin" may play some part in the intestinal phase of gastric secretion.

The Intestinal Phase of Gastric Secretion

Pavlov and others had observed that gastric secretion may be excited from the intestine, but it remained for Ivy and his associates to investigate this phenomenon and to elucidate its physiological significance. For this study they used dogs provided with Pavlov gastric pouches and isolated intestinal loops of the Thiry type, as well as animals in which the entire stomach had been isolated, the esophagus being joined to the duodenum. In the former group, the test substances could be placed in the intestine at will and the effect of this on the secretion of the miniature stomach observed; with the latter technique it was possible for the animal to ingest and swallow food in the usual manner but without passage of the food through the stomach; thus the purely gastric phase of secretion was eliminated. As an example of the most striking results obtained, we may cite the observations of Lim, Ivy and McCarthy[74] made on dogs with an isolated stomach. When cooked ground meat, bread, and milk are fed, the stomach pouch does not begin to secrete for from two to four hours. If the food is predigested with pancreatin or pepsin and hydrochloric acid, the entire stomach pouch secretes within an hour after feeding. The effect of drinking water seems to depend to a large extent on the degree of thirst and the time since the last meal, the shorter the time since the last meal, the greater being the stimulation. Mechanical distention of the intestine proves to be ineffective. Such observations support the view that the intestinal phase of gastric secretion is mediated by the absorption of secretin-like materials, products of digestion or specific hormones or both, from the intestine, and passage of them to the stomach by way of the blood stream. Finally, Ivy and Farrell succeeded in transplanting into the mammary gland a gastric pouch the original nervous and vascular connections of which had been severed. Such a transplanted pouch secretes a gastric juice containing free acid from two to six hours after a meal. This would seem to constitute proof that a humoral mechanism is concerned in gastric secretion. As Ivy himself points out, it does not, however, prove or disprove a hormone or a secretagogue mechanism. Ivy and his associates suggest that gastric secretion may in some way be related to an increased blood flow in the gastric vessels alone. Secretion is always associated with hyperemia of the stomach, and it is conceivable that the gastric glands are sensitive to an effective increase of blood flow through the organ.

It is not intended that this volume deal with clinical problems, but it will not be out of place to mention some of the practical implications of these researches on the intestinal phase of gastric secretion. For example, the hypernormal secretion that is associated with pylorospasm or pyloric stenosis can be adequately explained in the following manner (Ivy). The retention of food in the stomach leads to an augmentation of the gastric and intestinal phases

of gastric secretion. The gastric phase is augmented by an increased mechanical stimulation coincident with enhanced motility and blood flow, and by more prolonged action of secretagogues that are naturally present in such food substances as meat, or that result from digestion in the stomach. The intestinal phase is augmented because the chyme is more completely hydrolyzed, as the result of its retention in the stomach, so that when it is ejected into the duodenum it is more readily and rapidly digested. This more rapid digestion in the intestine means an increase in the concentration of secretagogues acting on or by way of the intestinal mucosa. Other factors known to play a rôle are the amount of diarrhea, the time of action of the chyme in the intestine, the amount of intestinal putrefaction, the degree of change of permeability of the intestinal mucosa, and the amount of passive as contrasted with active hyperemia. In other studies, Ivy[38] makes the suggestion that clinical cases of gastric hypersecretion should be examined for possible pancreatic dysfunction, because it has been shown that absence of pancreatic juice from the duodenum is associated with a more continuous secretion of gastric juice.

Gastric Chalone

Fat has been shown to exert a distinct inhibiting influence on the secretion of gastric juice; cream takes considerably longer to be digested than milk, and the presence of oil in the stomach delays the secretion of juice poured out on a subsequent meal of otherwise readily digestible food. Lim and associates[69] have succeeded in showing that this inhibitory action of fat is brought about through a humoral mechanism, the active agent passing into the blood stream when the fat comes in contact with the mucosa of the upper intestine. Since this agent is inhibitory in its action, it cannot be called a hormone, because this term signifies a stimulating agent; therefore the term *chalone* has been introduced as the name for an inhibitory substance elaborated in one tissue and passing by way of the blood stream to another tissue where it exerts its inhibitory action (see Chapter LXIX). Such an agent acting on the stomach might be called a gastric chalone. Greengard, Gray and Ivy[52] have extended the work in this field and concentrated the chalone sufficiently to be able to produce an experimental achlorhydria lasting from one to five hours. Their product, which they have called *enterogastrone,* was also found to cause some inhibition of gastric motility.

Quantity of Gastric Juice Secreted

In the light of what has already been presented concerning the various phases of gastric secretion, and the stimulating and inhibiting factors that may operate, it is evident that the amount of juice secreted in response to meals and in disease can be quite variable. According to Carlson, the total amount of gastric juice secreted in man on an average meal composed of meat, bread, vegetables, coffee and milk, and dessert, amounts to about 700 ml., being divided into 200 ml. in the first hour, 150 in the second, and 350 ml. during the third, fourth, and fifth hours. These figures were estimated partly on the basis of observations made on the man with the gastric fistula, and partly from the data supplied by Pavlov's observations on dogs. Estimates based on observations on dogs with the Pavlov miniature stomach are always subject to some reservations. More recently, Dragstedt and Ellis[33] have succeeded in preparing an isolated entire

stomach with intact vagus supply; such animals were observed to secrete from 1000-2600 ml. daily, the glands being able to secrete in response to stimuli even when the blood chloride concentration had been reduced to less than one-third of the normal value and there was extreme alkalosis. These authors express the belief that the failure to reabsorb the secreted gastric juice is the chief cause of death in high intestinal and pyloric obstruction, acute dilatation of the stomach, paralytic ileus in general peritonitis, gastrocolonic fistula, duodenal and gastric fistulas and profuse vomiting from other causes. The effective treatment for this loss of gastric juice was found to be simple replacement therapy by parenteral administration of large amounts of Ringer's solution daily.

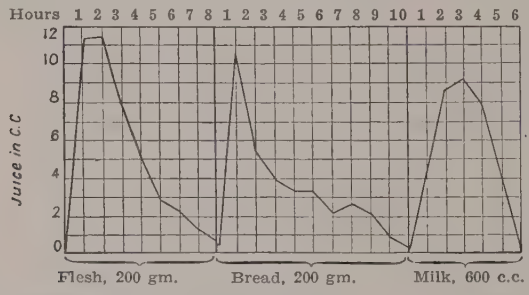


Fig. 328.—Cubic centimeters of gastric juice secreted after diets of meat, bread, and milk. (From Pavlov.)

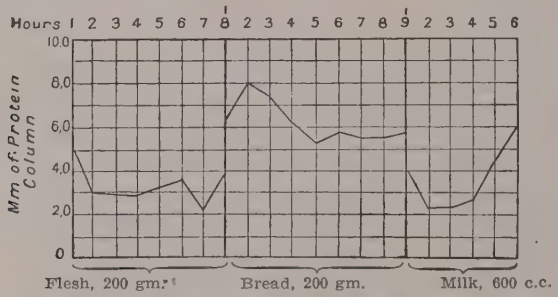


Fig. 329.—Digestive power of the juice, as measured by the length of the protein column digested in Mett's tubes, with diets of flesh, bread, and milk. (From Pavlov.)

The observations of Pavlov on the responses of gastric pouches of dogs to meat, bread, and milk have been widely quoted. They are interesting because they constitute evidence that the operation of the gastric secretory mechanism is not without some power of adaptation to the materials to be digested. In Figs. 328 and 329 are shown the results reported by Pavlov. It will be noted that the meal of meat called forth the secretion richest in acid, and the bread was most effective in stimulating the secretion of pepsin; also, the responses to bread and to milk were more sustained (compare curves in Fig. 329 for the fifth and succeeding hours) suggesting that these foods are more effective during the intestinal phase. These differences in responses with respect to acid and enzymes suggest that two separate secretory mechanisms may be involved, one concerned

in the elaboration and discharge of the hydrochloric acid, and the other in the secretion of pepsin and other enzymes. This is supported by the work of Babkin[5] and associates[114, 116, 117, 118] and Gilman and Cowgill[47] showing that the drug histamine stimulates only the acid-secreting mechanism. Whether this is true for man has been debated, but the carefully controlled studies of Toby[115] indicate that such is the case. This has naturally stimulated efforts to devise new gastric function tests useful in determining which of the two fundamental secretory processes may be deranged in pathological cases. The supposition that a satisfactory test might be based on the use of histamine and pilocarpine has proved to be erroneous because the amount of pilocarpine required to secure adequate stimulation of the pepsin-secreting mechanism is toxic. It has been found, however, that the hypoglycemia induced by injection of insulin is accompanied by stimulation of the vagal centers in the brain and a resultant secretion of gastric juice comparatively rich in pepsin.[6] Similarly, the vagal secretory centers can be stimulated by amino acids circulating in the blood[100, 101, 70] thus explaining in large measure the so-called intestinal phase of gastric secretion. This participation of the parasympathetic secretory innervation explains why the concentration of pepsin is higher in the gastric secretion of what Babkin calls the chemical phase[6] than in that obtained after histamine administration. The application of histamine and insulin in gastric function tests in man has been described by Babkin.[7]

THE INTESTINAL SECRETIONS

Pancreatic Juice

The secretion of pancreatic juice is studied by making a fistula of the duct, but, because of cicatrization, it is by no means easy to keep the fistula patulous. The secretion is almost absent during fasting, but starts in a few minutes after food is taken and increases in volume as more and more chyme enters the duodenum. In experimental animals the discharge of acid chyme from the stomach activates the secretin mechanism. The acidity of this chyme cannot, however, be the only excitatory cause for the secretion, for it occurs even in cases of achlorhydria where, possibly, it is due to the secretion of bile. The work of Mellanby[89] suggests very definitely that the presence in the intestine of bile, particularly the bile salts, promotes the flow of pancreatic juice, but the observations of Dragstedt and Woodbury[35] do not support this view.

McClure, Huntsinger and Fernald[84] have obtained samples of what they consider to be the bile, pancreatic juice, and gastric juice in the human duodenum following intraduodenal administration of pure foodstuffs and inorganic substances. From their study it was concluded that the concentrations of bile and pancreatic juice present in the duodenum vary with the type of stimulant administered, that the acid of gastric contents is not the essential factor in stimulating the secretion of concentrated bile and pancreatic juice thus contradicting the idea that acid is a specific and sole stimulant for the production of secretin, and finally, that cottonseed oil and peptone stimulate the liver and pancreas through secretagogic influences. Magnesium sulfate solution proved to be a much more potent stimulant of pancreatic secretion than hydrochloric acid.

This, as well as other work by McClure and associates also showed that fat is the most efficient stimulant of pancreatic enzymes and that the protein diges-

tion products are next in order, thus indicating a selective action on the processes of the pancreatic cell by which the different ferments are produced. In view of the good evidence for the existence of at least two separate secretory processes in the stomach (Gilman and Cowgill[47] and others[14, 116, 118, 120]) these findings of McClure et al., concerning the pancreas are not unintelligible. As indicated in the previous section, in which the adaptation of the gastric secretory response to the foods was discussed, we may consider that there is also some evidence supporting a similar adaptive capacity of the pancreas to the material presented for digestion. This is contrary to the older view, that the pancreatic juice remains very constant with regard to its content of the various ferments, the chief variation being with respect to the total amount secreted. It is obvious that the proof of this view must rest largely on the use of much more delicate analytical methods for measuring enzyme activity than those employed previously.

This contradiction of results obtained in animals with those yielded by human beings doubtless means that neither the acid-secretin mechanism nor the alternative possibilities should be taken as representing the entire truth to the exclusion of the other. It also indicates the importance of having at hand a satisfactory test for pancreatic secretory function which can be carried out easily under clinical conditions. If some dye or other readily detectable substance could be found, which upon injection is selectively eliminated by way of the pancreatic secretion, it might be made the basis of such a test. However, Crandall, Oldberg and Ivy[29] tested ninety dyes and could not find a single one that might be used.

The Bile

Composition.—Associated with the pancreatic juice in all its functions is the bile. When this fluid is prevented from entering the intestine, the digestive process becomes very imperfect, the absorption of fat being particularly interfered with (see page 975). Bile is also an excretory product, and its composition therefore is much more complex than that of the other digestive fluids. This varies considerably, however, according to the method of collection. Bile from the gallbladder after death contains much more solid material, particularly bile salts and mucin, than that collected from a fistula of the bile duct or gallbladder during life. These differences will be evident from Table CVI.

Table CVI

	BILE FROM	
	EXCISED GALLBLADDER	FISTULA OF COMMON BILE DUCT
100 parts contain—		
Water	86	97
Solids	14	3
Organic salts (bile salts)	9	0.9-1.8
Mucin and bile pigments	3	0.5
Cholesterol	0.2	0.06-0.16
Lecithin and fat	0.5-1.0	0.02-0.09
Inorganic salts	0.8	0.7-0.8

In general, it may be said that bile obtained from a fistula of the common bile duct in man contains only about 3 per cent of total solids, of which from one-fourth to one-half are inorganic, whereas bile obtained from a freshly excised gallbladder, and presumably, therefore, similar to the material occurring in the

viscus normally, contains from 10 to 20 per cent of total solids, of which only about one-twentieth are inorganic. The chief cause of this difference appears to be that when the bile goes to the intestine, a considerable proportion of its bile salts is reabsorbed into the portal blood and resecreted by the liver. Some of the difference may also be caused by the fact that absorption of water takes place from the gallbladder, and that mucin and possibly cholesterol are secreted by this organ. These striking differences between fistula and gallbladder bile are observed only when the common bile duct is occluded. If the bladder fistula is made with the common bile duct left open, some of the bile gains entry to the duodenum and therefore becomes reabsorbed and resecreted. It is well known that a fistula of the gallbladder in man closes after a time and the bile again takes its usual course along the bile duct into the duodenum.*

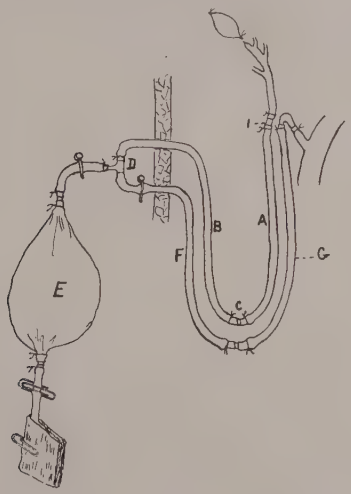


Fig.—330.—Diagram of altercursive intubation. A glass cannula (1) is inserted in the bile duct after ligating the cystic duct. It is connected by thin-walled rubber tubing, *A*, with thick-walled tubing, *B*, by means of a glass union, *C*. The thicker tubing passes through a narrow fistula in the abdominal wall and is attached to one limb of a T-piece, *D*, the central branch of which connects with a rubber bag, *E*. The remaining limb connects with another piece of thick tubing, *F*, going through a second fistula, and joined in the abdomen to thin tubing, *G*, attached to a cannula in the bile ducts near the duodenum. (From McMaster and Elman: J. Exper. Med. **41**: 529, 1925.)

Quantity of Bile Secreted and Factors Influencing It.—Interesting observations have been collected on the amount of the secretion from a fistula, both in man and in the lower animals. In man it is commonly stated that about 500 ml. of bile are secreted daily, the amount varying considerably during the different hours of the day. The secretion of bile is greatly reduced by hemorrhage. It is greater on a meat diet than on one of carbohydrates. It is reduced during starvation, but continues to be secreted up to the moment of death.

All estimates of bile flow based on observations of the discharge through a fistula, whether in man or animals, are subject to error depending on whether all bile is being diverted from the intestine or not. If it is, then the organism

*Further details concerning the chemistry of bile will be found on page 975.

cannot be maintained in a good state of health for very long; fat absorption is impaired, excessive intestinal putrefaction occurs, and anemia and other symptoms including even changes in the bones develop. Obviously, therefore, the use of a technique which permits observations of the flow during desired experimental intervals, with flow of the bile into the duodenum at other times, is desirable. The most suitable experimental procedure for accomplishing this seems to be that devised by Rous, McMaster and Elman[108] and called "altercursive intubation." A diagram showing the principles of this method is given in Fig. 330.

The gallbladder is tied off, a cannula introduced into the bile duct and connected with a piece of sterilized, flexible rubber tubing which is attached by a bent glass tube to a thicker piece of rubber tubing going through a stab fistula in the abdominal wall. The tube emerging from the fistula is connected with a T-piece, the central limb of which goes to a rubber bag for collecting the bile. The remaining limb of the T-piece is connected with tubing which goes through a second fistula in the abdominal wall to the duodenum. If the tubes be inserted with proper aseptic precautions, the animals can be kept in good health for several months, provided the bile is allowed to enter the intestine most of the time. It might be thought that the cannula in the bile ducts would soon become loose through necrosis of the walls beyond the ligature, but this is not the case. After a week or two, scar tissue closely embracing the cannula becomes developed around the duct. Even when the pressure of bile is raised to the maximum by obstruction of the bile ducts, no leakage occurs at this union of duct and cannula (Rous and McMaster and Elman[108]).

It has been found that the bile is always being secreted but in varying amounts under different conditions. For example, it becomes much lower during fasting and it also becomes greatly reduced if the bile is not allowed to reach the intestine. The secretion occurs quite independently of the nerves of the liver, for it persists after all of these have been cut. Normally the pressure in the bile ducts is low, but it increases considerably when these are obstructed and may rise to a height of about 300 mm. of bile when, however, the secretion suddenly ceases and reabsorption of bile takes place into the blood, resulting in jaundice. After taking a meal of meat or fat, the rate of secretion increases in about an hour and reaches a maximum in about five hours. Carbohydrate food, on the other hand, has no influence. The changes in the rate of secretion of bile therefore run more or less parallel with the secretion of the pancreatic juice. Reference has already been made to the conflicting observations of Mellanby,[89] and Dragstedt and Woodbury[35] on the question of a causal relationship of bile acids in the duodenum to the flow of pancreatic juice. There is no question, however, that pancreatic secretin promotes the flow of bile. When attempting to evaluate the numerous factors concerned in the stimulation of bile flow, the student should make a careful distinction between cholagogic activity—true stimulation of the secretory process in the liver—and factors which promote the discharge of bile by stimulation of the muscular wall of the gallbladder. Another distinction worthy of emphasis concerns the adequacy and accuracy of the experimental technique employed. Observations made on human beings with the tip of a swallowed tube in the duodenum cannot be as significant in elucidating the fundamental mechanisms as those made on animals under conditions where numerous important variables can be suitably controlled. Most of the substances which were formerly believed to be cholagogues have since been shown to act on the gallbladder musculature causing the viscus to contract, and not upon the secretory

process in the liver cells. Bile itself is probably the best of the known cholagogues; injection of it results in prompt elaboration and discharge of bile by the liver.

The Gallbladder.—In view of the anatomic arrangements it is evident that the bile collected from the common bile duct may be that newly formed by the liver cells or it may represent a discharge from the gallbladder. The prevalence of gallbladder disease in human beings makes it important to know as much as possible about the fundamental processes taking place in this organ. With regard to the functions of this viscus, Ivy summarizes the extensive literature on the subject as follows: *the gallbladder serves as a "factor of safety" in digestion,* and also as *a "factor of safety" in regulating the pressure in the biliary passages.* Bile is secreted practically continuously, but because of the sphincter located at the end of the common bile duct, this bile cannot flow at all times into the duodenum; it may therefore be stored in the gallbladder and thus be made available for intestinal digestive processes when required. The proved ability of the gallbladder to concentrate the bile means that its storage capacity is increased correspondingly. The facts that the ingestion of fatty foods brings about evacuation of the gallbladder more rapidly and completely than other foods, and that bile salts play an important rôle in the digestion and absorption of fats, in the promotion of bile formation, and in favoring intestinal motility, all support this view as to the function of this organ. The stored bile, according to this theory, is analogous to the psychic or "ignition" gastric juice, and was called "ignition" bile by Pavlov. "But, just as 'ignition (psychic) gastric juice' is not essential for adequate digestion, 'ignition bile' may not be essential. As the psychic secretion of gastric juice is very probably one of the 'factors of safety' in digestion, gallbladder bile may be viewed as a 'factor of safety' in digestion, other factors being able to compensate to an adequate degree for its absence after cholecystectomy" (Ivy). The function of this viscus in the regulation of pressure in the biliary passages is of considerable importance, particularly in those species like man, which are provided with a powerful sphincter situated at the end of the common bile duct and capable of sudden closure. The gallbladder functions as an elastic bag connected to a system of tubes. Being able to concentrate bile rapidly and markedly, its effectiveness as an elastic reservoir is thereby increased. It may be described as "a pressure regulatory and storage reservoir of small volume but of large capacity," one that "is able to provide for varying rate of bile formation and for the exigency that the bile may not be able to escape into the intestine because of the resistance of the choledochoduodenal mechanism. Thus, the secretory activity of the liver may continue unhampered by the inhibitory effects of high intraduct pressures for a period of hours."* The fact that not all species are provided with a gallbladder is not as serious an argument against these views as appears on first thought, because in species without the viscus, the resistance encountered by bile at the end of the common bile duct is small, and the passage of bile is practically continuous. When the gallbladder is removed, it is found that the ducts dilate or that the sphincter mechanism at the choledochoduodenal junction relaxes in some manner.

Among the important factors found to cause emptying of the gallbladder is the presence of certain foods in the intestine. Fat and fatty acids are most

*Ivy: Physiol. Rev. 14: 85, 1934.

effective, proteins (meat) rank next, and carbohydrates are least potent; these agents produce this action through a humoral mechanism, for they are effective after all the nerves have been cut. Ivy and Oldberg[65] have succeeded in preparing extracts of the duodenal mucosa which cause contractions of the gallbladder on intravenous injection, and have called this hormone "cholecystokinin." Chemically, it appears to be closely related to pancreatic secretin. The contractions of the gallbladder may also be brought about in experimental animals through stimulation of nerves, the vagus conveying augmentor and the sympathetic, inhibitory impulses, but it is questionable whether the "normal" contraction and evacuation of the viscus involves an extrinsic nervous mechanism, because of the ease with which fat placed in the duodenum can bring about emptying of the completely denervated gallbladder. The peculiarities of the reaction of the gallbladder to foods have been made the basis of certain practical suggestions for the clinic. The individual who has a tendency to formation of gallstones would do well to eat only a few meals a day, at least one of which contains an appreciable amount of fat, and thus supply at least once a day a vigorous stimulus to gallbladder emptying with the result that stones still small enough to be passed without pain are forced out. If many meals are taken at frequent intervals the stimuli for emptying are operating more or less continuously and the viscus at no time is given an unusually powerful one. On the other hand, in a patient with a fistula, healing of the fistula is improved by avoiding the continual oozing of bile, and this may be accomplished by feeding frequently with the result that the choledochoduodenal sphincter is kept open and bile flows readily into the intestine.

The discovery by Graham et al., that various nontoxic halogenized dyes, when injected, are excreted by way of the bile, combined with the fact that the concentrated dye in the gallbladder is opaque to the x-rays, has led to the technique of *cholecystography* for obtaining shadows of the gallbladder and biliary passages for diagnostic use in clinical medicine. Tetraiodophenolphthalein has been found to be particularly useful in this connection.

Intestinal Juice

The secretion of intestinal juice, or succus entericus, can obviously be studied only after isolating portions of the intestine and connecting them with fistulas of the abdominal wall. It appears here again that both a nervous and a hormone mechanism exist. Mechanical stimulation of the mucous membrane causes an immediate outflow of intestinal juice, the purpose of which under normal conditions is to assist in maintaining the fluidity of the bowel contents. This mechanically evoked juice does not contain any enterokinase and only small amounts of the other enzymes. Further evidence for nervous control of the secretion of intestinal juice has been obtained by isolating three pouches of intestine between ligatures, and then denervating the central pouch by carefully cutting all the nerves without wounding the blood vessels. On returning the pouches to the abdomen and leaving them several hours, it has been found that the middle pouch becomes distended with secretion, whereas the two end pouches remain empty. If the pouches are left for several days in the abdomen, however, the secretion from the denervated portion disappears again. A possible explanation of the result is that the nerves under normal conditions convey impulses to

the intestinal glands, which tonically inhibit their activity. This phenomenon is very much like the paralytic secretion of saliva (see page 894).

The existence of hormone control is best evidenced by the behavior of transplanted loops of intestine, such as those prepared by Nasset, Pierce and Murlin;[97] the presence of food in the digestive tract was accompanied by an increased rate of secretion by the loop not only of fluid but of the enzymes as well. The enzymes found in the intestinal juice are maltase, lactase, sucrase, erepsin, enterokinase, nuclease, phosphatase, and lipase. Nasset[95] has prepared from the small and large intestines of several animal species extracts shown to be potent excitants of the glands of the small intestine. These extracts were free from histamine, evidenced by a lack of influence on blood pressure, and from secretin, shown by their failure to excite the pancreas. *Enterocrinin* (intestinal secretagogue) has been proposed as a name for this hormone.

Other agents which have been demonstrated to promote the flow of intestinal secretion are histamine, pilocarpine, and the crystalline preparation of secretin isolated by Agren[1] (see page 896).

CHAPTER LXII

MECHANICAL FACTORS OF DIGESTION

MASTICATION, DEGLUTITION, VOMITING

In addition to the secretion of digestive juices purely mechanical factors operate in the alimentary tract in the handling of food. Many foods require some degree of comminution to reduce them to a size compatible with swallowing. It is necessary for the ingested material to pass through the thorax in order to reach the stomach and intestines. After digestion has occurred in the stomach the food must be passed on to the intestine. Sometimes it is important that the swallowed substance be prevented from leaving the stomach, that it be rejected entirely, and in order to meet this situation the mechanism of vomiting operates. Physical mechanisms are required for these processes. It is now our purpose to describe these mechanical factors of digestion.

Mastication

This process occurs in the mouth through the cooperation of the teeth and the muscles of the jaws. By the movements of the lower jaw on the upper, the two rows of teeth come together so as to serve for biting and crushing the food. The resulting comminution of the food forms the first mechanical step in digestion. The up-and-down motion of the lower jaw results in biting by the incisors, and after the mouthful has been taken, the side-to-side movements enable the grinding teeth to crush and break it up into fragments of the proper size for swallowing. The most suitable size of the mouthful is about 5 ml., but this varies greatly with habit. After mastication, the mass weighs from 3.2 to 6.5 Gm., about one-fourth of this weight being due to saliva. The food is now a semifluid mush containing particles which are usually less than 2 mm. in diameter. Some, however, may measure 7 or even 12 mm.

Determination of the proper degree of fineness of the food is a function of the tongue, gums, and cheek, for which purpose the mucous membrane covering them is supplied with very sensitive touch nerve endings. The sensitiveness of the tongue, etc., in this regard explains why an object which can scarcely be felt by the fingers seems to be quite large in the mouth. If some particles of food that are too large for swallowing happen to be carried backward in the mouth, the tongue returns them for further mastication.

The saliva assists in mastication in several ways: (1) by dissolving some of the food constituents; (2) by partly digesting some of the starch; (3) by softening the mass of food so that it is more readily crushed; and (4) by covering the bolus with mucus so as to make it more readily transferable from place to place. The composition of saliva varies according to the nature of the food (page 902). In some animals, such as the cat and the dog, mastication is unimportant, coating of the food with saliva being practically the only change which it undergoes in the mouth, in man the ability to bolt the food can readily be acquired, not, however, without some detriment to the efficiency of digestion as a whole. Soft

starchy food is little chewed, the length of time required for the mastication of other foods depending mainly on their nature, but also to a certain degree on the appetite and on the size of the mouthful.

It cannot be too strongly insisted upon that the act of mastication is of far more importance than merely to break up and prepare the food for swallowing. It causes the food to be moved about in the mouth so as to develop its full effect on the taste buds; the crushing also releases odors which stimulate the olfactory epithelium. On these stimuli depend the satisfaction and pleasure of eating, which in turn initiate the process of gastric digestion (see page 905).

The benefit to digestion as a whole of a large secretion of saliva, brought about by persistent chewing, has been assumed by some to be much greater than it really is, and there has existed, and indeed may still exist, a school of faddists who, by deliberately chewing far beyond the necessary time, imagine themselves to thrive better on less food than those who occupy their time with more profitable pursuits. These faddists usually assume that prolonged chewing insures more complete digestion of food by the saliva. In this connection it is pertinent to remark that salivary digestion can and does take place in the normal stomach for as much as a half-hour before the concentration and mixture with the acid of the gastric juice inactivates the ptyalin. This is due to the fact that each swallowed bolus tends to be placed in the center of the mass already in the stomach (see page 935), and some time is required before it comes to be the outer layer of the mass where it is in contact with the acid gastric secretion. In view of this fact, long-continued chewing would seem to be of no advantage.

Deglutition or Swallowing

This process is quite complicated and is best understood as occurring in three stages. The *first stage* is voluntary in nature and consists in the manipulation of the food in the mouth and preparation of it for passage into the upper part of the esophagus. After being masticated the food is rolled up into a bolus by the action of the tongue against the palate, and after being lubricated by saliva is moved, by elevation of the front of the tongue, toward the back of the mouth. It is very difficult or impossible to swallow dry material. The importance of proper flow of saliva and its admixture with the dry substance is thus emphasized. Psychic inhibition of salivary secretion as a result of great emotional stress, with a resultant inability to swallow a dry morsel, was made the basis of the so-called "trial by ordeal" in the Middle Ages, where an individual charged with a crime was forced to attempt to swallow dry flour or similar material. Interesting details of this process by which the morsel of food is manipulated in the mouth by the tongue are presented in Fig. 331, taken from the observations of Mosher.[94] It will be noticed that by approximation of the tip of the tongue to the roof of the mouth, escape of the bolus through the oral opening is prevented; also, the sudden movement backward of the posterior half and base of the tongue furnishes a propulsive force useful in driving the bolus through the pharynx into the upper end of the esophagus, the next stage of the process. Fig. 332 indicates the mechanism of swallowing as set forth by Barclay,[11] who believes that the movement of the tongue just mentioned is not the only force operating to insure passage of the bolus through the pharynx, but that suction plays a role, the negative pressure arising as a result of the elevation of the larynx and the back-

ward movement of the tongue. *Dysphagia in the first stage* is brought about by any factor which interferes with these manipulative movements of the tongue, or the failure to secure proper concomitant secretion of saliva.

The *second stage of swallowing,* a purely involuntary process, is essentially a complicated coordinated reflex act. It involves the passage of the bolus from the back of the mouth through the pharynx into the esophagus. It begins when the bolus, by stimulating sensory nerve endings (Fig. 333), acts on nerve centers located in the medulla oblongata so as to cause a coordinated series of contrac-

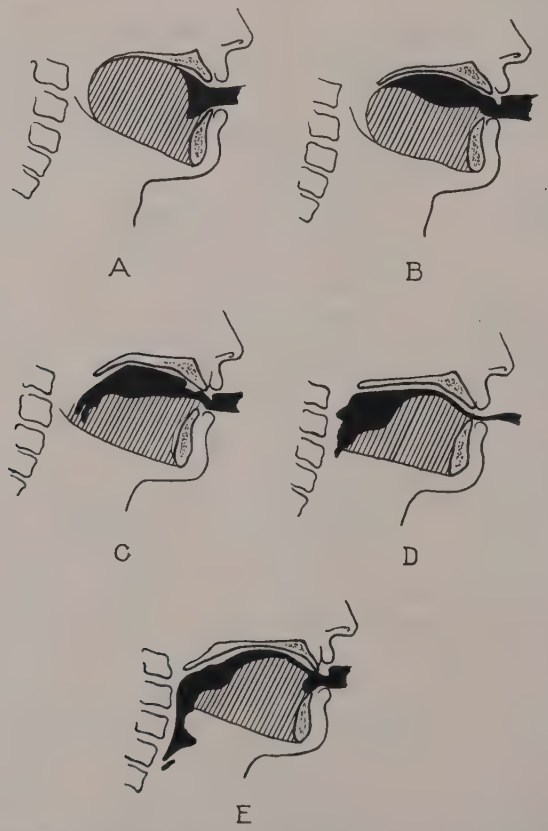


Fig. 331.—Drawings of a series of retouched tracings of x-ray films showing the movements of the tongue in swallowing.

A. The tip of the tongue is depressed and the barium accumulates above and in front of the tip of the tongue and behind the teeth.

B. The tip of the tongue comes up and the dorsum of the tongue sinks.

C. The tip of the tongue remains up. The dorsum and the base sink. The dorsum of the tongue becomes an inclined plane which slants downward from before backward.

D. The anterior half of the tongue rises as a globular mass to the roof of the mouth. The base of the tongue is depressed further. The individual now has the maximum mouthful.

E. The anterior half of the tongue remains at the roof of the mouth. The posterior half and the base of the tongue rise and are seen under the fluoroscope to shoot suddenly backward, driving the barium quickly down the pharynx. (Redrawn from H. P. Mosher: Laryngoscope 37: 235, 1927.)

tions of the muscles of the pharynx and larynx and an inhibition for a moment of the respiratory center. At the beginning of the second stage there is a slight inspiratory contraction of the diaphragm—the so-called respiration of swallowing—and the mylohyoid muscles quickly contract, with the result that the bolus

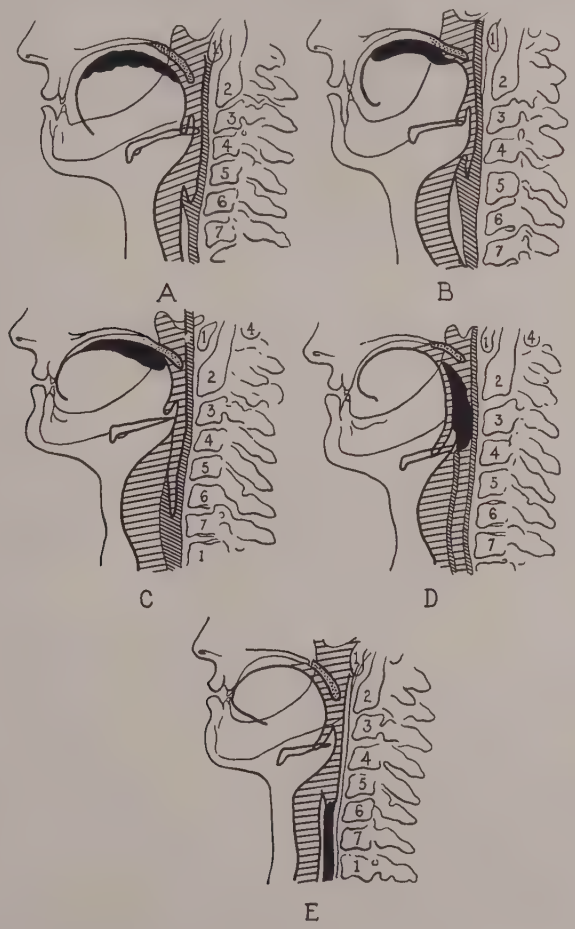


Fig. 332.—Stages in the swallowing process.

A. Before swallowing; bolus lies in the curve of the tongue. The figure shows the beginning of the act of swallowing. The bolus is compressed and the soft palate thrown against the posterior wall. The larynx is rising with the hyoid and the pharynx is narrowed.

B. Bolus compressed, nose closed off, larynx raised, pharynx and upper larynx obliterated.

C. Pharynx opening up, laryngeal pharynx drawn up to epiglottic position. Esophagus is an open tube and upper larynx is open again.

D. Pharynx open; laryngeal pharynx is in epiglottic position and food drops over epiglottis into open esophagus. Food caught on the epiglottis is deflected down aryepiglottic folds.

E. Laryngeal pharynx and esophagus drop with contents back to normal position. Bolus looks like a big drop in space. (After Barclay from Alvarez: *An Introduction to Gastro-Enterology,* New York, 1940, Paul B. Hoeber, Inc.)

passes rapidly between the pillars of the fauces into the upper end of the esophagus. At the same time the larynx is slightly elevated.

The movements thus brought about are designed to insure that the bolus shall pass into the upper end of the esophagus and not through any of the other passages which open into the pharynx, such as the nares, the larynx, and the chamber of the mouth. The soft palate becomes elevated, thus closing the opening into the nose; the posterior pillars of the fauces approximate so as to shut off the mouth cavity; and, in about a tenth of a second after the mylohyoid has contracted, the larynx is further pulled upward and forward under the root of

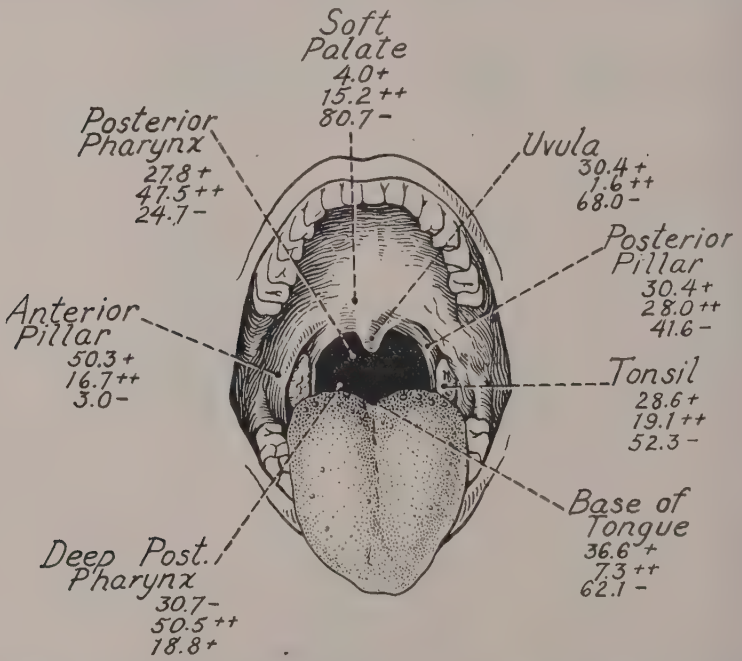


Fig. 333.—A drawing of mouth, tongue, and pharynx showing the positions of the several trigger zones, stimulation of which reflexly produces swallowing. The plus (+) sign indicates a swallowing reflex in response to a light stimulus over a small area. The double plus (++) sign indicates a swallowing reflex which occurred only in response to a stronger stimulation over a larger area. The minus (–) sign indicates no response. The figures represent percentages of results obtained in a study of 126 individuals. (Redrawn from Pommerenke: Am. J. Physiol. 84: 36, 1928.)

the tongue, which by being pulled backward becomes banked up over the laryngeal opening. This pulling up of the larynx brings its upper opening near to the lower half of the dorsal side of the epiglottis, and the laryngeal pharynx is pulled up with it. Swallowing is impossible unless the larynx is free to move. As a further safeguard against the entry of food into the air passages, the laryngeal opening is narrowed by approximation of the true and the false vocal cords. This is due to rotation of the arytenoid cartilages forward and inward so that the laryngeal opening becomes slitlike.

So far the force which propels the bolus is mainly the contraction of the mylohyoid, assisted by the movements of the root of the tongue. Now, however, a suction pressure is created in the pharynx by the larynx dropping and the tongue moving forward. This occurs while the pharynx is still pulled up so that the bolus readily enters it, after which it drops back to the normal position, thus allowing the larynx to open again. The bolus now readily enters the esophagus, which has become dilated on account of a reflex inhibition of the constrictor muscles of its upper end. This complicated coordinated movement of the second stage of swallowing involves, therefore, reciprocal action of various groups of muscles: inhibition of the respiratory muscles and of those that constrict the esophagus, and stimulation of those that elevate the palate, the root of the tongue, and the larynx. The entire process requires only about one-fifth of a second for its completion.

Dysphagia in the second stage may occur as the result of the action of any factor which interferes with this complicated reflex. Thus, the application of a local anesthetic to the appropriate receptors in the back of the mouth and pharynx will prevent the passage of nerve impulses to the swallowing center. Likewise, lesions involving the nerve paths through which the reflex is mediated can cause dysphagia in the second stage, and this dysphagia becomes a diagnostic sign of importance to the neurologist.

During the *third stage of deglutition* the swallowed food passes along the esophagus and through the cardiac sphincter into the stomach. The upper third of the esophagus contains cross-striated muscle fibers capable of rapid contraction; approximately the lower third is provided with smooth muscle only; the intermediate region contains a mixture of both types of muscle. The mechanism by which the food passes through the esophagus depends to some extent on the physical consistency of the food. The primary wave of peristalsis results from the pharyngeal stimulation and, in the case of a solid bolus that more or less fills the esophagus, there is produced a so-called secondary peristalsis due to local stimulation of the esophageal wall. The peristaltic wave travels down the esophagus in man at such a rate that it reaches the cardiac sphincter in about five or six seconds. On arriving here the cardiac sphincter, ordinarily contracted, relaxes for a moment so that the bolus passes into the stomach. In many animals, including man and the cat, the peristaltic waves travel much more rapidly in the upper part of the esophagus than lower down because of differences in the nature of the muscular coat. The purpose of more rapid movement in the upper part is no doubt that the bolus may be hurried past the regions where, by distending the esophagus, it might interfere with the function of neighboring structures, such as the heart. In other animals, as the dog, the muscular fiber is striated all along the esophagus, and the bolus of food correspondingly travels at a uniform, quick rate all the way. It takes only about four seconds for the bolus to reach the stomach of the dog.

Research has demonstrated that the harmonious sequence of contractions involved in the passage of the peristaltic wave along the esophagus depends upon an extrinsic nervous mechanism and not on a simple conduction of contractions from one portion of the muscular wall to another. The peristaltic wave of the upper part of the esophagus in the cat, and presumably in man, is transmitted by the esophageal branches of the vagus nerves. If these are severed, but the muscular coats are left intact, the esophagus becomes dilated above the level of the

section and contracted below, and no peristaltic wave can pass along it; on the other hand, the muscular coat may be severed (by crushing, etc.), but the peristaltic wave will continue to travel, provided no damage has been done to the nerves.

In the lower part of the esophagus, however, the wave of peristalsis, like that of the intestines, travels independently of extrinsic nerves. This has been observed in animals in which all of the extrinsic nerves have been cut some time previously. This difference between the upper and the lower portions is associated with the difference in the nature of the muscular fibers above noted.

The propagation of the wave by the nerves in the upper part of the esophagus indicates that the second stage and the first part of the third stage of swallowing must depend on impulses which come from the centers from which arise the nerve fibers to the pharynx, the larynx, and the upper levels of the esophagus. The discharges from the local centers are coordinated by a higher *swallowing center* situated in the medulla just above that of respiration, the afferent stimuli to which come from the pharynx by the fifth, superior laryngeal, and vagus nerves. The exact location of the sensory areas whose stimulation is most effective in initiating the swallowing reflex varies considerably in different animals. In man it is probably at the entrance to the pharynx; in the dog it is on the posterior wall. A foreign body placed directly in the upper portion of the esophagus of man has been observed to remain stationary until the individual made a swallowing movement. The afferent fibers in the glossopharyngeal nerve exercise a powerful *inhibitory* influence on the swallowing center as well as on that of respiration. Thus, if swallowing movements are excited by stimulating the central end of the superior laryngeal nerve, they can be instantly inhibited by simultaneously stimulating the glossopharyngeal, and the respiratory movements stop in whatever position they may be at the time. When the glossopharyngeal nerves are cut, the esophagus enters into a condition of tonic contraction, which may last a few days. This shows that the inhibiting impulses are acting continuously.

This inhibition of the esophagus is indeed a most important part of the process when liquid or semiliquid food is swallowed. By contraction of the mylohyoid muscle, fluids are quickly shot down the dilated esophagus, at the lower end of which, on account of the closure of the cardiac sphincter, they accumulate until the arrival of the peristaltic wave which has meanwhile been set up by stimulation of the pharynx. As the peristaltic wave approaches the cardia the sphincter becomes inhibited, allowing the fluids to be passed into the stomach. If the swallowing is immediately repeated, the esophagus remains dilated until peristalsis is inhibited and the fluid collects above the closed cardiac sphincter until the last mouthful is taken when the peristaltic wave passes over the esophagus and sweeps the contents through the sphincter which is at the same time relaxed. When a series of swallows in rapid succession, as in drinking, is made, the cardiac sphincter may remain inhibited throughout, so that the fluid passes directly into the stomach unassisted by the peristaltic wave. This mechanism does not of course operate when swallowed fluid must be raised against gravity as, for example, in the circus performer who takes a drink while standing on his head, or in the giraffe. In such cases, it is necessary for the liquid bolus to be moved along the esophagus by the peristaltic wave.

In addition to the reflex mechanism just described, it can be shown that secondary reflexes exist, and these are brought into play by stimulation of sensory fibers in the esophageal wall. These are of particular value when the primary reflex of swallowing is weak and results merely in forcing the food into the upper end of the esophagus. These reflexes are called forth with vigor whenever there is an obstruction of the esophagus: the presence of material above the obstruction results in a series of increasingly vigorous contractions, that operate to force the bolus against and through the obstruction if possible. Such contractions may be associated with considerable pain. In these secondary reflexes as well, the vagus nerve forms part of the nerve path involved. Sometimes a bolus is swallowed without having been sufficiently lubricated with saliva as, for example, in an individual who eats during a period of emotional stress and who therefore has some degree of psychic inhibition of salivary secretion. By vigorous effort he succeeds in forcing himself to swallow a dry bolus. Because of insufficient lubrication, the mass passes along the esophagus more slowly than usual with the result that it reaches the cardiac sphincter after it has opened and then closed. The bolus is then forced against the closed sphincter by the secondary reflexes in an attempt to pass the obstruction. During this period the individual may be conscious of considerable distress. After a short interval, however, the cardiac sphincter relaxes, the bolus is passed into the stomach, and the pain vanishes.

Dysphagia in the third stage results from any interference in the passage of the bolus through the esophagus. This may be due to purely mechanical causes, such as an enlarged thyroid gland, an aneurysm, neoplasms, traction exerted by scar tissue pulling the esophagus to one side thus rendering the passage more difficult, and cicatricial stenosis following ulceration due to corrosive poisons. It is obvious that dysphagia may also be the result of lesions involving the nerve paths through which the fundamental reflex is mediated.

The Cardiac Sphincter

The passage between the esophagus and the stomach is guarded by the cardiac sphincter or cardia. This exhibits a slight degree of tonus, superimposed upon which, from time to time, are rhythmic alternations of contraction and relaxation. This tonus is never very pronounced. In man it is said that a water pressure of 2 to 7 cm. applied to the esophageal side of the sphincter will drive air or water into the stomach, this pressure being less than that of a column of fluid filling the thoracic esophagus in the erect position. During repeated deglutition the tonus becomes less and less marked, and after a number of swallows the sphincter may become completely relaxed. When this relaxation disappears, however, the sphincter becomes more contracted than usual and remains so for a longer time.

The tonic condition of the sphincter is controlled by the vagus nerve, stimulation of which causes relaxation with an after-effect of strong contraction. The experiments of Brücke and Stern[16] may be cited as showing that the vagus carries inhibitory adrenergic fibers to the sphincter in contrast to the splanchnics which supply excitatory cholinergic fibers, stimulation of which can result in cardiospasm. Mechanical or chemical stimulation of the lower end of the esophagus increases the tonus of the sphincter. Forcing of the sphincter from the stomach side requires a higher pressure than from the esophageal. Eructa-

tion of gas, for example, does not take place until intragastric pressure has risen to about 25 cm. of water. In deep anesthesia, however, intragastric pressure may rise considerably higher without forcing the sphincter.

In animals fed with starch paste impregnated with insoluble salts of bismuth or barium and then examined by means of the x-rays, variations in degree of tone of the sphincter have been observed to be responsible for *occasional regurgitation of some of the gastric contents* into the esophagus up to the level of the heart and even to the base of the neck. The presence of the gastric contents in the esophagus starts a peristaltic wave, which pushes the material back again into the stomach. This peristaltic wave starts in the absence of any other phases of the deglutition process, indicating that it has been excited by the presence of the material in the esophagus itself, and belongs, therefore, to the lower order of peristaltic wave, as seen in the intestines but not in the upper half of the esophagus. The secondary reflexes described in the preceding section are doubtless involved here. Regurgitation of food into the esophagus occurs only when the intragastric pressure is fairly high. It may occur during a period of twenty to thirty minutes after a meal is taken, and disappear when the tonus of the sphincter becomes increased as a result of the presence in the gastric contents of free hydrochloric acid.

By listening with a stethoscope to the *sounds caused by swallowing,* it is usual to find that when a solid bolus is swallowed only one sound is heard, but with a liquid food there are two, one at the upper end due to the rush of the fluid and air, and the other at the lower end (heard over the epigastrium), four or five seconds later, due to the arrival of the peristaltic wave with the accompanying opening of the cardiac sphincter and the escape of the fluid and air into the stomach. Sometimes, when the person is in the horizontal position, this second sound may be broken up into several, indicating that, unassisted by gravity, the fluid does not so readily pass through the sphincter. The x-ray shadow yields results in conformity with the above. After swallowing milk and bismuth, for example, the shadow falls quickly to the lower end of the esophagus and then passes slowly into the stomach. When the passage of a solid bolus is watched by the x-ray method, its rate of descent will be found to depend on whether or not it is well lubricated with saliva; a well-lubricated bolus takes from eight to eighteen seconds.

Vomiting

The act of vomiting in the adult is a complex reflex act involving the muscles of the abdominal wall, the diaphragm, and the stomach itself. The early work of Magendie (1813) on this problem is most interesting. This investigator removed the stomach and substituted for it a bladder filled with fluid; injection of an emetic was followed by a typical vomiting movement resulting in ejaculation of the contents of the bladder. This, together with the fact, that vomiting cannot be brought about in a curarized animal owing to paralysis of the muscles of the abdominal wall by the drug (Gianuzzi) seemed to prove that the stomach itself plays a purely passive rôle during the act. X-ray studies have since demonstrated that such is not quite the case, but that the stomach by certain contractions does assist in the vomiting act.

Vomiting is usually preceded by a feeling of sickness or nausea, and is initiated by a very active secretion of saliva. The saliva, mixed with air, accumu-

lates to a considerable extent at the lower end of the esophagus, which it distends. A forced inspiration is now made, during the first stage of which the glottis is open so that the air enters the lungs, but later the glottis closes so that the inspired air is sucked into the esophagus which, already somewhat distended by saliva, now becomes markedly so. In the initial stages of the vomiting act a vigorous contraction occurs in the stomach at the incisura angularis; this separates the pyloric antrum from the fundic region which becomes a flaccid bag. The abdominal muscles then contract so as to compress the stomach against the diaphragm which is also contracted and, simultaneously, the cardiac sphincter relaxes, the head is held forward, and the contents of the stomach are ejected through the previously distended esophagus. After the contents of the stomach itself have been evacuated, the pyloric sphincter may also relax and permit the contents (bile, etc.) of the duodenum to be vomited. There are two important effects of the contraction of the diaphragm: the pressure brought to bear on the stomach in conjunction with the contractions of the abdominal muscles is greater, and the intrathoracic pressure is reduced thus allowing the esophagus to enlarge. It is an interesting fact that during the vomiting act there are no antiperistaltic contractions. Vomiting in the infant appears to be a more passive affair due most often to too great distention of the stomach by fluid, milk, for example.

Nervous Control of Vomiting.—The act of vomiting is controlled by a center located in the medulla, and the afferent fibers to this center may come from many different regions of the body. Perhaps the most potent of them come from the sensory nerve endings of the fauces and pharynx. This explains the tendency to vomit when the mucosa of this region is mechanically stimulated. Other afferent impulses come from the mucosa of the stomach itself, and these are stimulated by *emetics,* important among which are strong salt solutions, mustard water, and zinc sulfate. Certain other emetics, particularly apomorphine and to a lesser degree tartar emetic, act on the vomiting center itself, and can therefore operate when given subcutaneously. Afferent impulses causing vomiting may also arise from the abdominal viscera. Thus is explained the vomiting which occurs in strangulated hernia, and in other irritative lesions involving this region. X-ray observations have been made on the movements of the stomach of cats after the administration of apomorphine (Cannon). The first change noted is an inhibition of the cardiac end of the stomach, which becomes a perfectly flaccid bag. About the midregion of the organ, deeper contractions then start up, which sweep toward the pylorus, each contraction stopping as a deep ring at the beginning of the vestibule, while a slighter wave continues. A very strong contraction at the incisura angularis finally develops and completely divides the gastric cavity into two parts. On the left of this constriction the stomach remains completely relaxed, but at the right of it waves continue running over the vestibule. It is while the stomach is in this condition that the sudden contraction of the diaphragm and abdominal muscles ejects the cardiac contents into the relaxed esophagus. As these jerky contractions are continued, the gastric walls seem to reacquire their tone. Afferent impulses from the duodenal mucosa are even more potent for the initiation of the vomiting reflex than are impulses arising in the stomach itself (see Hatcher).

Pathological Vomiting.—Continuous or nearly continuous vomiting may occur in certain individuals who have established a vomiting habit because of the

ease with which the reflex may be conditioned. In such persons very slight stimuli may provoke a paroxysm of vomiting. Conditions such as the continuous vomiting of pregnancy, for example, belong in a different category; they must be due to the persistence of some etiologic factor. In the case of the illustration just cited, this factor may be continuous afferent impulses arising in the uterus and stimulating the center by reflex excitation. In view of what is known concerning the mechanism of vomiting, it is conceivable that such a condition may be due to a metabolic agent in the blood acting more or less continuously on the vomiting center. Some of the results of continuous vomiting are malnutrition of greater or lesser degree, constipation due to the partial starvation, and a degree of alkalosis varying with the extent to which the vomitus contains intestinal fluids as well as gastric secretion

CHAPTER LXIII

MECHANICAL FACTORS OF DIGESTION (Cont'd)

THE MOVEMENTS OF THE STOMACH

The Character of the Movements.—Even from the earliest days it has been recognized that the stomach performs two important functions: (1) receiving the swallowed food and then discharging it slowly into the intestine, and (2) initiating the chemical processes of digestion. In order to understand the mechanism by which the stomach collects and then discharges the food, it is necessary first of all to recall certain anatomical facts concerning the organ, and for this purpose it is most convenient to accept the description given by Cannon, which is illustrated in Fig. 334. The organ is divided into a cardiac and a pyloric portion by a deep notch in the lesser curvature, called the incisura angularis. The cardiac portion is further subdivided into two by the cardiac orifice. The part which in man lies above a line drawn horizontally through the cardia is the fundus. The part lying between the fundus and the incisura angularis is known as the body of the stomach which, when full, has a tapering shape. The pyloric portion lying on the right of the incisura angularis is further divided into three parts: the pyloric vestibule, the antrum, and the pyloric canal, the last of which forms the lumen of the pyloric sphincter and in man measures about 3 cm. in length (see Fig. 334). From a study of the development and structure and from a consideration of its behavior when examined radiographically Cole[25] believes that the ascending or first part of the duodenum virtually belongs to the stomach and should be so considered when the gastric movements are under investigation. Since this portion of the duodenum receives and retains the chyme for a short time after its egress from the stomach and in radiographs appears to surmount the pyloric sphincter, he has termed it the "reservoir cap" or pilleus ventriculi.

The filled stomach of a person standing erect is so disposed that the greatest curvature forms its lowest point, which may be considerably below the umbilicus. As digestion proceeds and the stomach empties, the greater curvature becomes gradually raised, so that ultimately the pylorus comes to be the most dependent part of the stomach. From these and many other observations it is certain that the emptying of the stomach does not at all depend on the operation of the force of gravity. Indeed, that this cannot be the case is perfectly clear when we consider the disposition of the stomach in quadrupeds.

Exact observations on the movements which the stomach performs from the time it is filled with food until it empties, have been made by the x-ray method, first introduced by Cannon.[18] The method consists in feeding the animal with food that has been impregnated with insoluble salts of bismuth or barium, then exposing it to the x-ray and either taking instantaneous photographs of the shadows or observing them by means of a fluorescent screen. In the accompanying figure (Fig. 335) the outline of the shadow cast by the cat's

stomach is shown for intervals of an hour each during digestion. Soon after the stomach has become filled, peristaltic waves are seen to take their origin about the middle of the body of the viscus, and to course toward the pylorus. The region above the origin of these waves—that is, the cardiac half of the body of the stomach and all the fundus, often called the cardiac pouch—is free from peristaltic waves but is the seat of a tonic contraction which, as digestion proceeds,

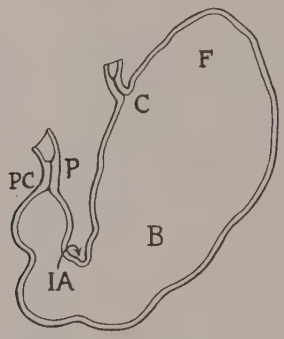


Fig. 334.—Schematic outline of the stomach. At *C* is the cardia; *F*, fundus; *IA*, incisura angularis; *B*, body; *PC*, pyloric canal; *P*, pylorus. The antrum is the portion from *IA* to *PC* inclusive. (From Cannon.)

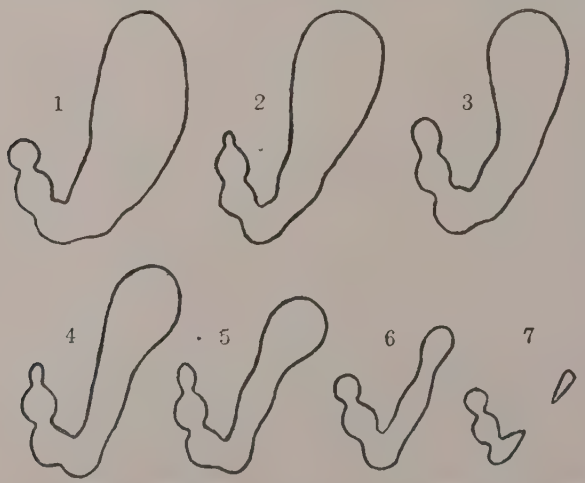


Fig. 335.—Outlines of the shadows cast by the stomach at intervals of an hour each after feeding a cat with food impregnated with bismuth subnitrate. (From Cannon.)

presses steadily with increasing force upon the mass of food and delivers it slowly to the lower and more active portion of the stomach.

As the food passes into the lower part of the stomach, the cardiac pouch becomes gradually reduced in size until finally, when the stomach is empty, its outline, as revealed by radiographs, departs from the pyriform shape characteristic of the full organ to assume a more or less tubular form.

From this description, it is evident that the function of the cardiac portion of the stomach is to serve as a reservoir for the food which by a slow contraction of the gastric wall is gradually delivered into the lower and more motile part of the stomach. The motor phenomena of this portion are of a complex nature and will now be considered.

Cole,[25] by the employment of serial x-ray photographs taken at short intervals has shown that this portion of the human stomach undergoes a succession of rapid changes in shape (Fig. 336), due to the peristaltic waves which course over it toward the pyloric sphincter. The pyloric region also exhibits alternate phases of increased and diminished tone while the waves are passing over it. The period of gastric activity intervening between a phase of complete relaxation and the reappearance of this phase is termed a gastric cycle. In some types of

Fig. 336.—Drawings made from skiagrams of the human stomach taken at intervals after food. A gastric cycle is illustrated. (After Cole.[24])

gastric motility a peristaltic wave takes but one gastric cycle to complete its journey from its origin to the pylorus. Such a wave would show in consequence one phase of complete relaxation and maximal contraction. In other types two, three or four gastric cycles may occur during the passage of the wave. The waves are therefore spoken of as one, two, three or four cycle types of peristalsis, respectively. It follows from this that at any moment the stomach will show one, two, three or four waves according to the particular type of peristalsis which is present. Cole considered four cycle to be the most common type whereas Alvarez reports that the three cycle is the most frequent; the rapid one cycle type is very rare.

The passage of a gastric cycle is from 2 to 3 seconds. The time required for the passage of a four cycle type of peristaltic wave from its origin to the pyloric

sphincter therefore will be from 8 to 12 seconds. It rarely exceeds 10 seconds. Following the cardiac analogy Cole divides the gastric cycle into a systole and a diastole. In the former, which occupies 7/10 of the cycle, the constrictions produced by the peristaltic waves are most marked. Diastole occupies 3/10 of the cycle and represents the period during which relaxation is taking place (Fig. 336).

The adaptation of the capacity of the normal stomach to the volume of its contents is remarkable. When the stomach of a living animal is distended by fluid, the intragastric pressure shows very little change even up to the point of rupture of the viscus (Grey[55]). After excision, the stomach loses in considerable measure this adaptive power.

The nervous control of the stomach movements is not entirely understood. An excellent idea of the complexity of these movements and the relatively enormous literature concerning them can be gained from a study of Chapter XV of Alvarez's monograph. There is considerable automaticity of the organ presumably dependent upon the rich nerve plexuses in its walls. Thus, coordination between the increasing tone of the fundus and the rhythmic contractions of the pylorus is probably dependent on Auerbach's plexus. More local movements, on the other hand, such as the advancing waves of the antrum, may be purely myogenic since they persist after the continuity of Auerbach's plexus has been destroyed, by making several circular cuts through the muscular coats of the stomach wall (Cannon). Of the extrinsic nerves the vagus seems to have a greater influence than the sympathetic, but the results which follow its stimulation vary considerably. They are unpredictable so far as the pylorus is concerned, and in the fundus they seem to depend very largely on the state of tone of the stomach at the time of stimulation (McSwiney and Wadge[88]), contraction occurring when this is low and relaxation when it is high. Stimulation of the vagus also causes the esophagus to contract. Stimulation of the sympathetic (splanchnic) usually causes diminution of tone and depresses the movements of the stomach.

Section of the vagi at a midthoracic level has been found to result in temporary paralysis of the lower portion of the esophagus where smooth muscle is present; if food is swallowed it distends the tube and the atonic walls fail to respond by contraction. A similar condition develops in the stomach; muscular tone is lost and there is an absence or marked depression of peristaltic activity. If food is introduced through a stomach tube, it may lie for hours undisturbed by any gastric motility. Later tone and motor activity reappear in the lower esophagus and swallowed food is passed into the stomach by peristaltic contractions. Gradually the tone and motility of the stomach walls return and after a few days the presence of food excites gastric peristalsis of normal type and vigor. The recovery of peristaltic activity seems dependent on the development of a state of intrinsic tone of the smooth muscle itself. Cannon made the important observation that severance of the vagi after food was taken does not seriously interfere with the digestion of that particular meal. He suggested that the stomach can exhibit a "psychic" increase in muscular tone which is a consequence of vagal excitation brought about by the pleasant taste of food. Both Cannon and Alvarez have likened this tonal phenomenon to the so-called psychic secretion of gastric juice which has been proved to require for its occurrence an intact vagus nerve supply. Alvarez has presented considerable clinical evidence that the pleasurable taking of food or even the anticipation of this experience may increase the tone and the motor activities of the entire gastrointestinal tract.

The evidence from experimental sectioning of the vagi indicates that an important function of these nerves is to set the smooth muscles of the lower esophagus and stomach in a state of continuous moderate contraction or tone upon which are superimposed the essential peristaltic contractions. These activities, however, can develop independently of the vagi

after their section. It is important to realize that the vagi are compound nerves and that there is evidence that all vagal fibers to the gastric musculature do not exert identical effects. For example Cannon and Lieb observed that whenever a swallowing movement occurs, the intragastric pressure drops. This "receptive relaxation" of the stomach, as they appropriately designated the phenomenon, denotes the presence of an automatic mechanism which lowers intragastric pressure while the esophagus is pushing new material through the cardia. Cannon states that this "reciprocal adjustment between the esophageal muscle and the gastric muscle wholly disappears after the vagus nerves have been severed." It follows that certain vagal fibers exert an inhibitory influence upon the gastric musculature.

It has already been stated that stimulation of the sympathetic supply to the stomach exerts an inhibitory influence upon the gastric smooth muscle. It also produces vasoconstriction in this region. Evidence has been obtained that no serious digestive upset follows complete removal of the sympathetic ganglia and chains in cats, dogs or monkeys (see Chapter XI) and it has long been known that bilateral splanchnic section does not appreciably affect gastric activities. Obviously the sympathetic supply does not contribute any essential factor to normal gastric motility or tone. It is, however, a factor in producing the inhibition of gastric secretion and motility which occurs as a result of painful stimulation or strong emotional excitement. This direct inhibition by nerve impulses is doubtless reinforced by the secretion from the adrenal medulla, which occurs under such conditions and which is itself a result of sympathetic activity (see Chapter XI). Further, Cannon and Murphy have shown that the splanchnic nerves are responsible for the retardation in the emptying of the stomach which occurs as a result of laparotomy and surgical handling of the stomach and intestines.

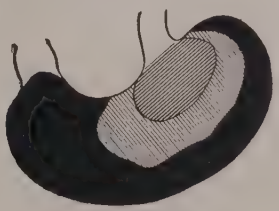


Fig. 337.—Diagram of a section through the frozen stomach (rat) some time after feeding three differently colored portions of food. (From Howell's Physiology.)

The Effect of the Stomach Movements on the Food.—This has been studied: (1) by dividing the food into portions that are differently colored and, after some time, killing the animal, freezing the stomach and making sections of it (see Fig. 337); (2) by making little pellets of bismuth subnitrate with starch and observing their behavior under the x-rays; or (3) by removing samples of the stomach contents by means of a stomach tube (Rehfuss tube) inserted so that its free end lies in either the cardia or the pyloric region. By the first of the above methods it has been found that first mouthfuls of food lie along the greater curvature, where they form a layer over which the subsequently swallowed food accumulates, with the last portions next the cardia. The pepsin and hydrochloric acid of the cardiac end, therefore, act soonest on the first swallowed portion of a meal, and the more recently swallowed central masses are not affected by the secretions for some time, so that opportunity is given for the saliva mixed with the food to develop its digestive action.

As has been shown by removing the stomach contents with a tube at various periods after feeding with starchy food, considerable amylolysis may go on for some time. When separate samples are removed in this way from the cardiac and pyloric parts, it has been found that for up to half an hour the contents of both have about the same percentage of sugar, but that for some time after this

interval the cardiac contents contain considerably more sugar than the pyloris. Later the percentages of sugar again become equal, no doubt on account of diffusion. The diastatic action in the fundus is finally brought to an end when the contents become completely permeated by the hydrochloric acid. In this connection it is worthy of note that the addition of hydrochloric acid up to the point of neutrality greatly accelerates the rate of diastatic digestion. As the outer layers of food in the stomach become partly digested on account of the action of the pepsin and hydrochloric acid, the food is slowly pressed into the active right half of the stomach, where by the action of the peristaltic waves it is moved on to the pyloric vestibule.

By observing the x-ray shadow cast by two pellets of bismuth subnitrate it has been noted by Cannon that, as the peristaltic wave approaches a pellet, it causes it to move forward more rapidly for a short distance, but soon overtakes it and in doing so causes the pellet to move back a little towards the fundus. This backward movement is less than the forward movement, so that after the wave has passed, the position of the pellet is a little forward of that which it would have occupied had there been no wave. The behavior of the pellet and, therefore, of the stomach contents, is very much like that of a cork floating at the edge of the sea; as each wave approaches, it hurries the cork on a little, but after its passage the cork recedes again until the second wave carries it still a little farther forward. As the peristaltic wave approaches the pyloric vestibule and becomes more powerful, its effect on the pellets becomes more marked.

These observations made on cats and other laboratory animals also apply in the case of man. Removal of the contents of the cardiac and pyloric regions separately with a stomach tube after feeding with a test meal of which a part was colored with carmine or charcoal, has shown that none of the coloring material was present in the contents of the pyloric end up to twenty minutes or so after the food had been taken. It then appeared but at first only in traces. Another important distinction between the food in the two portions of the stomach relates to its consistency. In the pyloric end it is semifluid and homogeneous in character; in the cardiac end, on the other hand, it is a lumpy, rather incoherent mass.

The gastric movements must greatly *facilitate the digestive processes* in the stomach. In the cardiac part the undisturbed condition of the food will, as we have seen, facilitate the digestive action of ptyalin, whereas in the body of the stomach the peristaltic waves, besides moving the food onward, will tend to bring fresh portions of mucous membrane and food in contact, so that the latter becomes more thoroughly mixed with the pepsin and hydrochloric acid. In the pyloric part, where no hydrochloric acid is secreted, the contents, already sufficiently acid in reaction, become more thoroughly churned up with the local pepsin secretion, so that proteolytic action progresses very rapidly. Little, if any, absorption occurs in the stomach.

The observations of Carlson, Ginsburg[49] and others indicate that the usually accepted explanation of the pains of gastric and duodenal ulcers; namely, corrosion and irritation of exposed nerve endings in the gastric and duodenal mucosae by highly acid stomach contents, is not correct. The pains of ulcer may be present when the contents of the stomach are alkaline and they may be absent when so-called hyperacidity exists. According to these authors the pains are analogous in origin to those of hunger, and are the result of contractions of the

stomach and duodenum, the nerves of which are in a hyperexcitable state. Hyperacidity, then, will affect the pain of ulcer only insofar as it increases the motility of the stomach.

THE EMPTYING OF THE STOMACH

The Control of the Pyloric Sphincter.—Pavlov originally advanced, and Cannon elaborated by experiment, the view that the acidity of the chyme constitutes the chief factor in the control of the pyloric sphincter. According to this idea, acidity on the stomach side of the sphincter causes it to open, whereas acidity on the duodenal side causes it to close, the latter stimulus being prepotent, so that food cannot leave the stomach so long as any remains unneutralized in the duodenum. Teleologically, this theory is a most attractive one; but, as Cannon himself pointed out there are certain known facts of gastric evacuation which do not conform with it. Thus, it fails to account for the rapid passage of water and egg white into the duodenum, and it leaves unexplained the normal emptying time of the stomach in certain pathological states in which the secretion is suppressed or greatly reduced (achylia). Cannon interpreted these and certain other facts as indicating that there are still other factors controlling the emptying besides that of acidity. When considering the controversy concerning Cannon's theory, it is well to bear in mind that Cannon's tests were made with food of normal consistency, and that he himself indicated his appreciation of the rôle of possible factors other than acidity. It has been shown that in addition to chemical stimulation, mechanical stimulation by the food masses adjacent to the sphincter is of great importance. In a general way, one may say that the sphincter obeys the law of the intestine (page 944), so that mechanical stimulation on the antral side causes it to open, whereas stimulation on the duodenal side causes it to close. Since the antral stimulation will be set up by the passage of peristaltic waves, their arrival at the sphincter will coincide with its relaxation. But this mechanism is complicated by the fact that stimulation by food in the duodenum is prepotent in the sense that it operates to prevent evacuation in the face of an opening stimulation arising in the antrum. It is apparently the "cap" or "caput" of the duodenum that is most sensitive in this regard, for as long as food remains here—and x-ray examination shows that it commonly remains for some time—evacuation does not readily occur as the peristaltic waves arrive from the antrum. The mechanism is still further complicated by the occurrence of more or less independent rhythmic contractions in the caput.

As a working hypothesis dealing with mechanical factors we may consider that the emptying depends upon the relative pressures of the contents of the pyloric antrum and the caput of the duodenum. When a strong peristaltic wave passes over the antrum it tends to open the sphincter and to raise the pressure of its contents above that in the caput so that some of the contents pass through before the wave reaches the sphincter, which then closes. Toward the end of digestion the tone of the sphincter relaxes so that regurgitation of food from duodenum to stomach may occur. The foregoing hypothesis, however, does not completely explain all of the observed facts; and, although space will not allow a complete review of the experiments relating to this problem, it may be useful to refer briefly to some of them.

From the study of serial radiographs in man Cole[25] observed that a definite relationship exists between the movements of the antrum and those of the pyloric

sphincter. The activities of the sphincter were found to be directly proportional to the magnitude of the antral contractions, and chyme passed into the duodenum during each of these but not in the intervals. Luckhardt, Phillips and Carlson[79] combining fluoroscopic observations with graphic records, obtained by means of a balloon inserted in the stomach, have also shown that the passage of chyme into the duodenum coincides with peristaltic waves traveling over the stomach. By observing the gastric contents collected from a duodenostomy opening made immediately below the pyloric sphincter it was noted that water placed in the stomach passed through the sphincter in gushes which was considered on the whole evidence of rhythm and it was assumed on this account that they were dependent upon peristaltic waves (Ivy). The water as it left the stomach was neutral in reaction. A more precise study of the interdependence of the antral and sphincter movements has been made by Wheelon and Thomas[122] who combined the study of radiographs with graphic records obtained by balloons placed in the antrum and pyloric canal. In this manner tracings could be taken of movements occurring simultaneously in the two regions. These observers found that when the peristaltic wave—commencing in the body of the stomach and

Fig. 338.—Tracings showing the relationship between contractions of the antrum (lower tracing) and the pyloric sphincter (upper tracing). Note that the antrum precedes the sphincter but that the latter contracts before the antrum has relaxed. (From Wheelon and Thomas.)

traveling over the vestibule—reaches the antrum the sphincter becomes relaxed so that any material swept forward by the constricting wave is free to pass through the pyloric opening. The wave is sufficiently broad to involve the whole antrum at one time and indeed it involves the sphincter before it has begun to disappear from the antrum with the result that for a short period the antrum and sphincter together are in the contracted state. Soon after this, the antrum enters upon its negative phase (relaxation) the sphincter being still contracted. These facts are shown in Fig. 338.

The foregoing studies are open to the criticism that the animals were anesthetized. The more recent observations of Thomas and associates[114, 115] were made in dogs provided with fistulae suitable for the insertion of the various balloons. In these experiments it was clearly demonstrated that as the gastric peristaltic wave approaches the pylorus there is, regularly, marked inhibition of the rhythmic contractions of the first 15 or 20 cm. of the duodenum. Recovery of activity in the duodenum begins at the same time as the contraction

of the pyloric sphincter that follows each gastric wave. The changes just described start at the pylorus and travel downward at a speed characteristic of the spread of descending inhibition (10 cm. per sec.) but more rapidly than ordinary peristalsis. In general, the gastric influence appears to be that of diminishing the activity of the part of the duodenum affected as compared to the activity of other unaffected parts. While food is being taken, it was observed that the contractions of the duodenum are inhibited along with those of the stomach. This work confirms that reported in 1910 by Joseph and Meltzer, who interpreted their findings as meaning that there is a receptive relaxation of the duodenum associated with each gastric peristaltic wave.

The recent studies of Meschan and Quigley[92, 103] are interesting in this connection. These workers used three tandem balloons located in the pyloric antrum, the pyloric sphincter, and the duodenal bulb in trained unanesthetized dogs, and showed that these three regions function together as a unit. Waves originating in the stomach were observed to pass successively over all three structures. Contrary to the generally accepted belief, the pyloric sphincter in these studies appeared to be passively relaxed most of the time, contracting only when a peristaltic wave reached it, this contraction being maintained while the wave continued over the duodenal bulb. It is obvious that such a contraction of the sphincter would operate to hinder regurgitation more than it does emptying. Vagotomy did not alter in any fundamental way this coordinated complicated relationship of antrum, sphincter, and duodenal bulb. The fact that the inhibitory effects on emptying of various substances placed in the intestine were greatly decreased or abolished by vagotomy indicates that these substances exert their influence through the enterogastric reflex. Thomas[113] has attacked this problem by measuring the pressures on the two sides of the pylorus in dogs provided with suitable fistulas. He observed cyclic changes in pressures associated presumably with the passage of a peristaltic wave; a complete cycle was most often observed when the stomach contained food; an incomplete cycle, characterized by lack of the initial rise of intragastric pressure, was most commonly seen when water was being evacuated. According to Crider and Thomas,[30] the acidity of the chyme in the intestine proves to be less important than the digestion products which may be present; proteoses accounted for about one-half of the inhibitory effect noted, peptones and other substances being responsible for the remainder.

It appears evident that the underlying mechanism controlling the emptying of the stomach is in some way related to the nervous one involved in the peristaltic contractions of the stomach. There is a suggestion that the movements of the antrum and pyloric sphincter follow the "law of the intestine" (page 944), perhaps with certain minor modifications. That some other factor also influences the emptying time is, however, certain. It is difficult, otherwise to account for the rapid passage from the stomach of water and egg white and the retention of other substances until they reach a more or less fluid consistency. It is likely that one important function of the stomach is to protect the duodenum as much as possible from hard discrete objects. A nervous mechanism with receptors in the antral wall responsive to unusual pressure stimulation of discrete small areas, such as would result from contact with hard objects contained in a large soft mass, might subserve this function. If the entire mass were soft, semifluid, with no hard particles in it, then contraction of the antrum should result in an equal distribution of the pressure through the operation of Pascal's principle.

Under such conditions, the mass in the antrum would be ready for discharge through the pylorus. Whether it would be so discharged could then depend upon the presence in the duodenum of the material discharged previously, as researches already suggest that this is a factor. If the mass has not been softened sufficiently, the above-described mechanism would operate to delay its discharge.

When there is food in the lower ileum and also in the stomach, the latter makes little effort to empty until the ileum has discharged its contents into the cecum. This is called the *ileogastric reflex*. When the vagus nerves are cut below the cardiac branches, much of the food remains for a long time in the stomach and is only slowly digested since the secretion of gastric juice is interfered with.

There is usually a considerable amount of *gas* in the part of the stomach above the entrance of the cardia, on account of which this part of the stomach has sometimes been called the stomach bladder. In the upright position this gas forms a bright area in the x-ray plate, but when the person reclines the gas spreads to a new location. Its presence may influence gastric digestion by preventing the contact of the food with the mucous membrane, and by interfering with the efficiency of the peristaltic waves in moving the food. Considerable gas therefore retards the emptying of the stomach, as has been shown experimentally by x-ray observations on animals in which feeding with the standard amount of food was followed by the introduction of air. It was noted that the air did not diminish the frequency or strength of the peristaltic waves, but that these could not act efficiently on the food. When the presence of gas is associated with atony of the stomach walls, the retardation in the discharge will, of course, be still more pronounced. The temperature of the swallowed food does not appear to have much influence on the stomach movements or on the rate of discharge from the organ.

Influence of Pathological Conditions on the Emptying of the Stomach.—An important surgical application of these facts concerns the *behavior of food after gastroenterostomy*. It has been thought that this operation would cause the food to be drained from the stomach into the intestine and thus leave the region of the stomach between the fistula and the pylorus inactive. This assumption is based on the idea, which we have seen to be erroneous, that gravity assists in the emptying of the stomach. As a matter of fact, if the gastroenterostomy is made when there is no obstruction at the pylorus, it has been found that the chyme takes its normal passage through the sphincter and, almost without exception, none leaves by the fistula. When the pylorus is partly occluded, the food sometimes passes in the usual way, and sometimes by the fistula. The cause for this predilection for the pyloric pathway depends on the pressure conditions in the gastric contents. Gastroenterostomy, therefore, is not likely to afford much relief except when gross mechanical obstruction exists at the pylorus.

Another objection to gastroenterostomy in the presence of a patulous pyloric sphincter rests on the fact that the food, after passing the sphincter and moving along the intestine, may again enter the stomach through the fistula. This is most likely to occur when the stomach is full of food, for under these conditions the stretching of its walls separates the edge of the opening, the intestine being drawn taut between the edges, so that the opening between the stomach and the intestine assumes the form of two narrow slits, which act like valves permitting the food to enter into but preventing its escape from the stomach. Only seldom under these circumstances can any food pass into the

intestine beyond the stomach opening. Repeated vomiting after gastroenterostomy has been observed in experimental animals only when obstructive kinks or other demonstrable obstacles were present in the gut, the obstruction being located in that part of the intestine beyond its attachment to the stomach.

When the pyloric obstruction is complete, food must, of course, leave by the fistula, digestion by the pancreatic juice and bile being still carried on because of the fact that bile continues to be secreted and it acts as a stimulus to the production of secretin (see page 895). Further provision for adequate digestion of food in such cases is secured as some of the food after leaving the fistula passes back for a certain distance into the duodenum where, however, it soon excites peristaltic waves, which carry it forward again. This insures thorough mixing with the digestive juices. From their experimental experience Cannon and Blake[19] recommend that, when the fistula must be made, it should be as large as possible and near the pylorus, and that the stomach afterward should not be allowed to become filled with food. To avoid kinking of the gut, they also recommend that several centimeters of the intestine should be attached to the stomach distal to the anastomosis.

CHAPTER LXIV

MECHANICAL FACTORS OF DIGESTION (Cont'd)

THE MOVEMENTS OF THE INTESTINES

The length of the small intestine and the size of the cecum of the large intestine vary considerably in different animals. In the carnivora, such as the cat, the small intestine is relatively short; in the herbivora, relatively long. Thus, it is about three times the length of the body in the cat, and four to six times in the dog; in the goat and sheep, it may be nearly thirty times the length of the body. In the carnivora the cecum is either absent or rudimentary, whereas in those herbivora which do not have a divided stomach the cecum is very large and sacculated, as is also the colon. The reason for the great size in herbivora is that practically the whole of the digestion of cellulose takes place in this part of the gut. This digestion, as we shall see later, does not depend on any secretion poured forth by the animal itself, but upon the action of bacteria and certain enzymes (cytases) that are taken with the vegetable food.

MOVEMENTS OF THE SMALL INTESTINE

The movements of the small intestine have been studied (1) by the bismuth subnitrate and x-ray method, (2) by observing them after opening the abdomen of an animal submerged in a bath of physiologic saline at body temperature, (3) by observing the changes in pressure produced in a thin-walled rubber balloon inserted in the lumen of the gut and connected with a recording tambour, and (4) by excising portions of the intestine and keeping them alive in a bath of oxygenated saline solution at body temperature.

The Segmenting Movements.—When a suitably fed animal is placed on the holder for examination by the x-ray method, no movement in the intestinal shadows is generally observed for some time. The first movement to appear is the breaking of one of the columns of food into small segments of nearly equal size. Each of these segments again quickly divides, and the neighboring halves suddenly unite to form new segments, and so on, in a manner which will be made clear by consulting Fig. 339. This *rhythmic segmentation,* as Cannon has called it, continues without cessation for half an hour or longer, and the food shadow does not meanwhile seem to change its position in the abdomen to any extent. The splitting up of the segment and the coming together of the neighboring halves proceed as a rule with great rapidity; thus, if we count the number of different segments during a definite period, we may find the rate of division in the cat to be as high as 28 or 30 per minute. In man the divisions occur at a frequency of approximately 10 per minute, which corresponds to the frequency with which sounds can be heard when the abdomen is auscultated. In certain animals, such as the rabbit, segmenting movements have not been observed, but instead of them there occurs a rhythmic to-and-fro shifting of the masses of food along the lumen of the gut; this is rapidly repeated for many minutes.

When the intestines are floated out in a warm bath of saline solution, it is seen that the rhythmic segmentation is caused by narrow rings of contraction.

Under such conditions also it is often noted that the loops of intestine sway from side to side. The balloon method also reveals the presence of slight waves of contraction that pass rapidly along the gut, and follow each other at the rate of 12 to 13 per minute. Both of the muscular coats of the intestine are involved in these contractions, and it is believed that they are responsible not only for the pendular movements but also for the rhythmic segmentation observed by the x-ray method. According to this view these movements are constantly passing along the intestine and become exaggerated by the mechanical stimulus which is offered by the masses of food which they therefore cause to be divided into portions.

Several functions can be assigned to these movements. They cause intimate mixture of the food with the digestive juices, and by bringing ever new portions of food in contact with the mucosa, they encourage absorption. They also have an important massaging influence on the blood and lymph in the vessels of the intestinal walls. Indeed, the passage of lymph from the lacteals into the mesenteric lymphatics seems to depend very largely upon these movements.

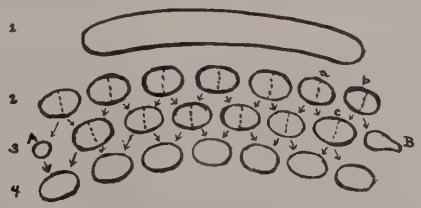


Fig. 339.—Diagrammatic representation of the process of segmentation in the intestine. An unbroken shadow is shown in *1* and its segmentation in *2*. The dotted lines across each mass show the position of division and in *3* is shown how new masses are formed by the split portions coming together. (From Cannon.)

The investigations of Alvarez[2, 3] and his co-workers show that the rhythmic intestinal contractions are not of uniform rate throughout the entire length of the small bowel, but vary in frequency inversely with the distance from the pylorus. For example, under the same experimental conditions the contractions of a duodenal segment proceed at a more rapid rate (17 to 21 per minute) than do those of an ileal segment (10 to 12 per minute). Associated with the variations in frequency are also differences in the amplitude of the contractions of the intestinal muscle. As the contractions become less frequent their amplitude increases. The tone and irritability of the intestine also diminish progressively from duodenum to ileum. According to Alvarez the underlying cause of the decline in contraction rate is to be found in a study of the metabolism of the intestinal muscle in the different regions. It was found that the respiratory metabolism (output of CO_2, use of O_2) of an excised strip, whether contracting or rendered quiescent by adrenalin, was greater the higher its origin in the small intestine. This direct relationship between the frequency of rhythm and the metabolic rate of intestinal muscle favors the view that the intestinal contractions are myogenic; this is supported by the further experimentally determined fact that the application of cocaine or nicotine does not abolish the contractions. Moreover, the graded activity of the muscle with regard to rhythm, tonus, and irritability is probably an important factor in the production of peristalsis and in the determination of the direction which this movement shall take.

The Peristaltic Movements.—The other movement observed in the small intestine is that known as the *peristaltic wave.* It occurs in two forms: (1) as a slowly advancing contraction (1 to 2 cm. per minute), preceded by an inhibition of the walls, and proceeding only through a short distance in a coil (4 to 5 cm.); and (2) as a swift movement called the *peristaltic rush,* which sweeps without pause for much longer distances along the canal.

Further analysis of the peristaltic wave can readily be made by the balloon method (Fig. 340). If the gut is pinched above the balloon, a marked relaxation occurs over the latter, and this relaxation extends for about two feet down the intestine. If, on the other hand, the gut is pinched a little below the balloon, a long-continued contraction occurs over the latter. The conclusion we may draw from this result is that the stimulation of the gut causes contraction above the point of stimulus and relaxation below, this being known as "the law of the intestine"—(Bayliss and Starling). We have seen that it applies also in the case of the cardiac and pyloric sphincters. In this connection it is of interest to report the observation by Alvarez[2] who was able to insert a balloon into an intestinal fistula in man; when the inflated balloon attached to a string was not allowed

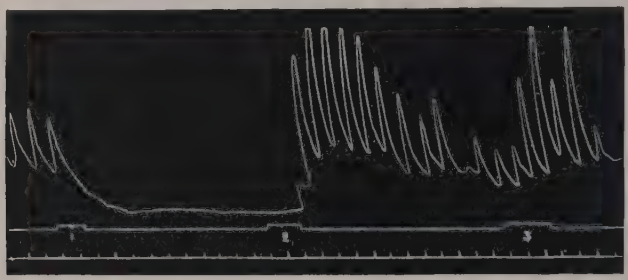


Fig. 340.—Intestinal contractions (balloon method) after excision of the abdominal ganglia and section of both vagi. Mechanical stimulation above (*1*) and below (*2*) the balloon causes relaxation and contraction respectively. (From Starling.)

to move with the peristaltic wave because the string was held taut, the patient soon experienced distress; evidently more vigorous contractions were produced in an endeavor to push the balloon forward and these were associated with symptoms of colic.

Carey[22] has made a study of the longitudinal and circular fibers of the wall of the small intestine and has found that they are arranged in a spiral manner; in excised loops a bolus was seen to move forward in a counterclockwise spiral path when viewed from the cephalic end. Reid, Ivy and Quigley[106] recently studied this matter in dogs provided with Thiry-Vella intestinal loops (loops both ends of which open through the body wall), and confirmed the report of Carey under a variety of physiological conditions. A similar conclusion was reached in studies where the x-ray method was employed. This rotational propulsion is apparently the same in the jejunum and ileum, and in these experiments was not altered by alimentation or by various drugs.

The Physiological Nature of the Rhythmic and Peristaltic Movements.—Much investigative effort has been expended in a study of the fundamental

mechanism involved in these intestinal movements. It has been found that the rhythmic segmentation type of movement is not affected by the application of cocaine or nicotine. Inasmuch as these drugs paralyze nervous structures it has been concluded that the rhythmic movements are myogenic in origin. The most recent work tends to confirm this opinion. Gunn and Underhill and later Alvarez and Mahoney recorded rhythmic contractions of small strips of the circular layer of intestinal muscle which were free from ganglion cells. Although it is possible that some nerve fibers from Auerbach's plexus remained in these preparations it seems most improbable that these disconnected axons supplied rhythmic stimuli to the smooth muscle cells. The peristaltic contractions, on the other hand, probably depend upon a local nervous structure, since they are paralyzed by the application to the gut of cocaine or nicotine. This local nervous system no doubt resides in Auerbach's plexus which must therefore be considered complex enough to direct nervous impulses so as to bring about a relaxation of the gut in front of the stimulus and contraction above it.

Nervous Control of the Movements.—The influence of the central nervous system on the intestinal movements has been studied by the usual methods of cutting and stimulating the extrinsic nerve supply. Through the splanchnic

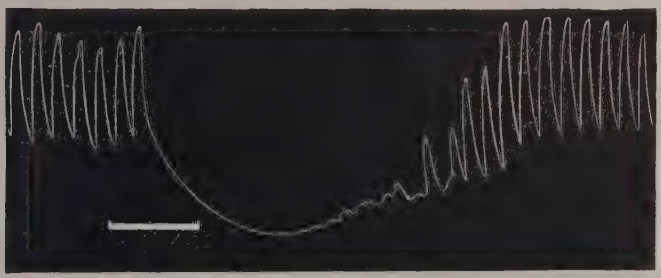


Fig. 341.—The effect of excitation of both splanchnic nerves on the intestinal contractions. (From Starling.)

nerves *inhibitory* impulses are conveyed to the intestine (except the ileocolic sphincter), so that after they have been severed the movements become more distinct. Indeed, in many animals after opening the abdomen no intestinal movement can be observed until the splanchnic nerves have been cut. Stimulation of the peripheral end of the nerve inhibits any movement which may be in progress (Fig. 341). The impulses through the vagus nerves are of an opposite character. Section of these nerves has little effect on the motility of the small intestine, but stimulation causes contraction (Fig. 342). Stimulation of a sensory surface even in an anesthetized animal will often inhibit the intestinal movements. After section of the splanchnics this inhibition does not occur.

By observing the rhythmic contractions of an isolated strip of the small intestine suspended in a bath of oxygenated saline solution at body temperature, it can readily be shown that the presence of even a minute trace of epinephrine is sufficient to produce complete inhibition of the movement. The parallellism between the effects of splanchnic stimulation and those of epinephrine is very significant, for it may be that the marked inhibition of intestinal movement which

occurs during fright and anger is the result of an increased secretion of this hormone from the adrenal glands (see page 171).

The circular muscular coat of the last two or three centimeters of the ileum before it joins the cecum is definitely thicker than the rest of this coat, indicating that it has a sphincter-like action. This *ileocolic sphincter,* as it is called, opens when food is pressed against it from the ileum, but remains closed when food is pressed against it from the cecum. It therefore obeys the law of the intestine. That it is physiologically distinct from the musculature of the rest of the ileum is indicated by the fact that the splanchnic and vagus nerves do not affect it in the same way; thus, stimulation of the splanchnic causes a strong contraction of the sphincter, whereas stimulation of the vagus has no effect.

Peristalsis is much more rapid in the duodenum than in other parts of the small intestine. During the first stages of digestion, the food ordinarily lies

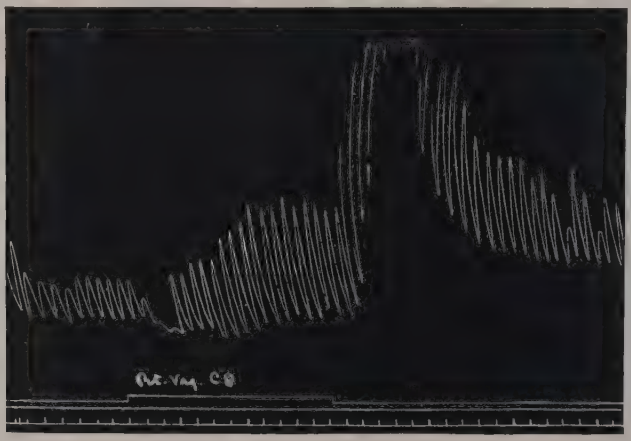


Fig. 342.—The effect of stimulation of right vagus nerve on the intestinal contractions. (From Starling.)

mainly in the right half of the abdomen, and later in the left half. There is considerable variation in the time that elapses before it enters the colon. In the cat, carbohydrates reach this part of the gut in about four hours.

The stimulation of the vagus nerves to the small intestine is probably associated with the production of a chemical agent which serves in the transmission of the nervous impulse, according to the recent work of Bunting[17] and associates. These investigators prepared denervated intestinal loops to be used as an indicator of the presence of acetylcholine or similar substances, and found that stimulation of the vagus was followed by contraction of the test loop. Evidently, therefore, the small intestine must be included in the structures provided with parasympathetic nerves which are cholinergic (see page 181).

Effect of Certain Clinical Conditions on the Movements.—Studies have been made of the effect of various surgical procedures on peristalsis and intestinal motility in general. The fact that peristalsis in the small intestine is in one direction, namely, toward the ileocolic valve, is readily demonstrated by separat-

ing a segment of the intestine, reversing it, and then suturing to restore continuity of the gut. If the reversed segment is less than about three inches long, little difficulty is experienced in the passage of material through it; if the segment is longer, its peristalsis now directed toward the stomach may be powerful enough to produce all the symptoms of intestinal obstruction.

After an *end-to-end anastomosis* of the gut, no evidence can be obtained by the x-ray method that any hesitation occurs in the movement of the shadows at the anastomosis. On the other hand, when a lateral anastomosis is established, stagnation of the food in the region of the junction may occur. The end of the proximal loop beyond the opening is also in danger of becoming filled with hardened material. Another objection to lateral anastomosis depends on the fact that in performing the operation a considerable amount of the circular muscle is cut, which interferes with peristaltic activity.

Observations have also been made by the x-ray method on the behavior of the intestinal contents following *intestinal obstruction.* It has been observed that as material collects in the gut just above the obstruction, strong peristaltic waves are set up, which move the food toward the obstruction so powerfully as to cause the walls of the canal in front to become bulged, until at last the pressure causes the contents to be squirted back through the advancing ring of peristaltic contraction. These waves succeed one another rapidly.

The type of peristalsis known as the peristaltic rush can be induced experimentally in animals by intravenous injection of ergot. It probably also occurs in conditions of abnormal irritation of the gut in man, and is believed to be the characteristic activity of the gut after administration of a strong purge.

MOVEMENTS OF THE LARGE INTESTINE

In considering the movements of the large intestine in man and their nerve control, it is necessary, as insisted on by Garry, to realize that observations made on laboratory animals may give but uncertain guidance, owing to the marked differences in the relative development of its various parts in different animals. In herbivores the proximal colon and cecum are large and sacculated; in carnivores they are small and simple tubes, and in omnivores the structure is intermediate between these two. The colon of man is sacculated in its ascending, transverse, and descending limbs, approximating the herbivorous rather than the carnivorous type, and the longitudinal muscular coat does not become continuous until the caudal part of the pelvic colon is reached. The pelvirectal flexure has a sphincterlike action, absent in the gut of laboratory animals, although in the dog there is constriction about 5 cm. craniad to the anus, above which the walls have a high degree of tone and below it are lax. The ileocolic junction has a true sphincter (Fig. 343).

It is impossible at present to give a clear description of the innervation of the lower bowel. Two factors are clear, viz., that the intrinsic nerve plexuses run parallel in their development with that of the muscular layers and that there is no sharp distinction of function between so-called sympathetic and parasympathetic fibers. Indeed, the effects of section or stimulation of a given nerve structure may give unlike results in different animals, even of the same species. The innervation for cat and man as far as is known is outlined in the accompany-

ing diagram (Fig. 344), but details concerning the exact functions of the various nerves in man must await the observations of surgeons in the operating theatre. (For a further description of these nerves and the literature, see the review by Garry.)

Quite apart from the dissimilarity in the anatomical arrangement of the nerves, it is most difficult to obtain consistent indications of their functions because these are affected by numerous influences, such as anesthesia, opening of the abdomen, and the degree of distention of the gut with food. The decerebrate animal is probably the most satisfactory preparation to use, but even this is open to objection because influences transmitted from suprabulbar regions are missing.

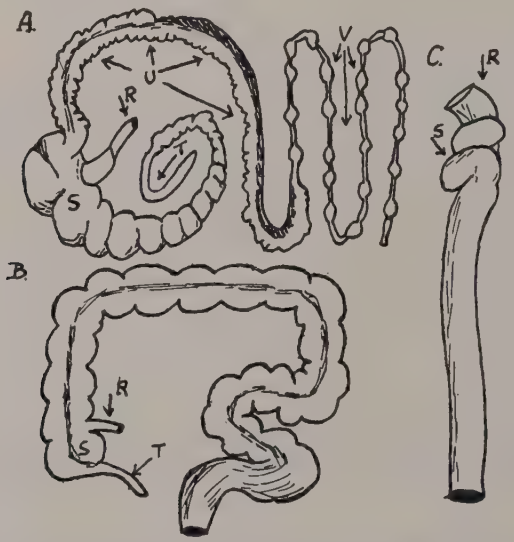


Fig. 343.—The large bowel. *A*. In the rabbit: *R*, ileum; *S*, cæcum; *T*, appendix; *U*, proximal colon; *V*, distal colon. *B*. In man: *R*, ileum; *S*, cecum; *T*, appendix. *C*. In the dog; *R*, ileum; *S*, cecum. (After Garry.)

Experimental investigation of the nature of the nerve control is best obtained by observing the effects of section; electrical stimulation of nerve trunks is of little value because it differs so widely from the normal and may involve simultaneous excitation of fibers exercising opposed effects, but mechanical stimulation, by distending a suitable balloon placed in the gut, gives useful information, and its effects and those of other procedures can be recorded by connecting the balloon with a tambour.

Opinions conflict with regard to the degree of autonomy of the large bowel. The proximal portions undoubtedly possess this to a much greater degree than the distal, the movements of the latter being normally dependent on the extrinsic nerve supply and disappearing after destruction of the lumbosacral regions of the cord. After a time which varies greatly in different animals, movements may return after decentralization, and defecation may occur at regular

intervals, but of course without any voluntary control. There is no evidence for supposing that there are extraspinal centers for the act of defecation.

The tone of the internal anal sphincter, composed of unstriped muscle, is maintained by fibers from the inferior mesenteric ganglia; after their section the whole anal canal dilates. The external sphincter is composed of a peculiar form of striped muscle—small fibers rich in sarcoplasm—and the relaxation which follows when its nerves are cut or the cord is destroyed disappears afterward, which has led some to believe that it can be controlled by local nerve ganglia. For striped muscle the external sphincter is peculiarly resistant to curare. There

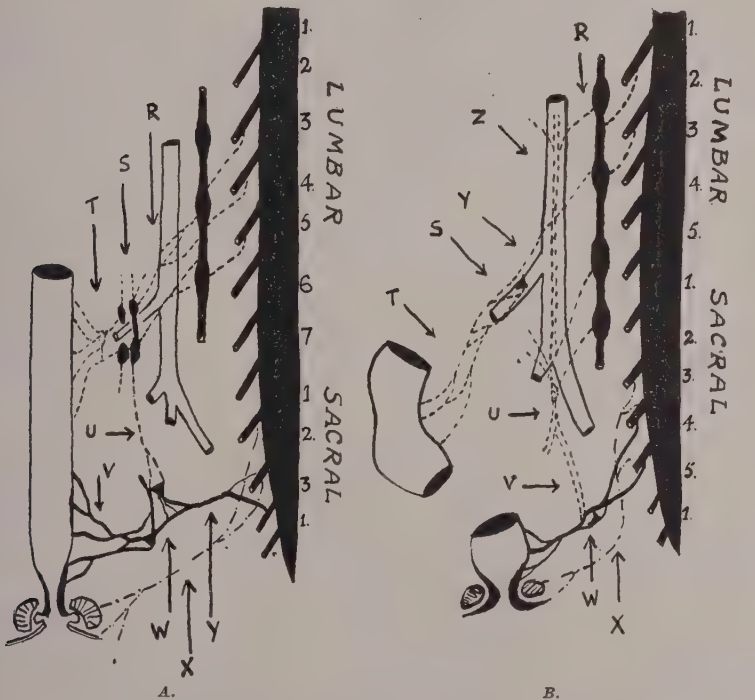


Fig. 344.—Nervous outflow to the distal colon (*A*) in the cat, and (*B*) in man.

A: R, spinal rami to inferior mesenteric ganglia; *S,* inferior mesenteric ganglia; *T,* lumbar colonic nerves; *U,* hypogastric nerve; *V,* sacral colonic nerves; *W,* pelvic plexus; *X,* pudendal nerve; *Y,* pelvic nerve.

B: R, pelvic splanchnic nerves; *S,* inferior mesenteric plexus; *T,* inferior mesenteric nerves; *U,* presacral nerve; *V,* hypogastric nerve; *W,* hypogastric plexus; *X,* pudendal nerve; *Y,* intermesenteric nerve; *Z,* intermesenteric plexus. (After Garry.)

is a defecation center in the lumbosacral region of the spinal cord and its activities are under the control of a higher center in the medulla. After spinal section between these two centers in man, defecation is paralyzed until spinal shock (page 88) has passed off when it returns as a purely reflex act. Section of the lumbar outflow of nerves leads to increased activity of the colon, as also does spinal anesthesia. These nerves seem to control the postural tone of the

bowel (Learmonth and Markowitz). Their section also causes relaxation of the internal anal sphincter. The sacral nerves have a motor influence and their section is followed by loss of tone of the colon. They also convey afferent impulses.

The importance of a knowledge of the functions of the various nerves is unquestioned from the surgical standpoint since most satisfactory results are often obtained by cutting them in Hirschsprung's disease (inhibition of the colon and contraction of the internal anal sphincter occurring in infants). It is possible that increased knowledge may point the way as to which nerves should be cut in certain cases of intractable constipation.

Apparently the movements are much the same in the cat as in man. As the food passes through the ileocolic sphincter into the cecum and accumulates there, it gradually sets up, by its pressure, a contraction of the muscular walls of the gut somewhere about the junction between the ascending and transverse colon. This wave of contraction then begins to travel slowly toward the cecum without, however, being preceded by any relaxation of the wall of the gut, as is the case with a true peristaltic wave. This first wave is soon followed by others, with the result that the food is kept in the cecum, being meanwhile prevented from passing into the ileum by the operation of the ileocolic sphincter and by the oblique manner in which the ileum opens into the cecum. These waves continue for three minutes or so; then the colon becomes passive and more material enters it from the ileum. These antiperistaltic waves, however, are not usual in man, but frequent small contractions may be seen in the cecum and ascending colon. The effect of the movements is to knead and mix the intestinal contents, and thus encourage the absorption of water from them.

In man also a massive peristaltic wave occurs three or four times a day driving the contents from the proximal into the distal portion of the colon, and the fecal matter collects proximally to the pelvirectal flexure. Some of it passes into the rectum as a result of one of the large peristaltic waves, and as a consequence the defecation reflexes are set up. The descending colon itself is never distended with contents and merely serves as a tube for transferring the masses from the proximal to the distal colon.

THE PELVIC COLON

By the time the distal colon is reached (6 to 8 hours after leaving the stomach), the intestinal contents have become definitely fecal in character; and they consist of indigestible matter (cellulose, etc.), bacteria, which are largely dead, the products of bacterial action, and some of the constituents of the bile. Two types of peristaltic waves have been observed in the distal colon: a slow movement, and what Holzknecht calls "large colonic movements" which serve to carry in a few seconds the intestinal contents through the greater part of the large intestine. The latter are analogous to the peristaltic rush movements of the small intestine. The "large" movement has been observed in man, particularly after a meal and, when related to the taking of a meal has been spoken of as the "gastrocolic reflex," which is most evident after the first meal of the day. If defecation is performed shortly after the urge due to this reflex is evident, the eliminatory act may usually be performed without undue effort. It is quite possible that these "large" movements also occur as part of the defecation act

itself, especially where this is accompanied by a subjective impression that emptying has been fairly complete. These movements are probably responsible for the discharge of soft or solid feces, which occurs at regular intervals one to three times a day, through fistulae placed distal to about the middle of the transverse colon.

DEFECATION—THE LAXATION PROBLEM

Defecation is partly a voluntary and partly an involuntary act. When material reaches the rectum, the pressure probably produces the desire to defecate. The involuntary part consists in large peristaltic movements in the descending and pelvic colon, which empty their contents into the rectum, and a relaxation of the two anal sphincters allowing the material to be evacuated. The voluntary act consists mainly in a contraction of the muscles of the abdominal wall; this contraction, together with forced inaction of the diaphragm by closure of the glottis, greatly increases the intra-abdominal pressure which aids in forcing the colonic contents into the rectum.

Mechanism of Defecation.—The underlying mechanism of defecation is undoubtedly an involuntary reflex. There is a center in the lumbosacral region of the spinal cord, and a higher center located in the medulla. As justification for the belief that an involuntary reflex is involved, one may cite Goltz's dog in which the entire spinal cord was removed except the cervical and upper thoracic segments. This animal, after recovering from the operation, defecated in normal fashion once or twice a day, indicating the existence of an intrinsic mechanism sufficient for consummating the act. The involuntary character of defecation in young infants is well known. The anal sphincters are normally in a state of vigorous contraction. It is difficult to state the extent to which this inhibition is entirely involuntary. The external sphincter, being composed of cross-striated muscle, is dependent for its tone on somatic nervous impulses and is under the control of the will. When the nerves are destroyed, the tone disappears and incontinence of feces results, but after some time the tone is reacquired independently of nervous impulses. The internal sphincter is composed of involuntary muscle supplied by autonomic nerves coming through the inferior mesenteric ganglia. The circumstances under which fecal incontinence so frequently occurs, particularly in aged people and in young untrained children, suggest that while inhibition normally occurs as part of the complicated reflex it is especially susceptible to cerebral influences, that is, to conditioning.

As material collects in the lower bowel, the tone of the musculature adapts itself to the volume of the contents, so that very considerable accumulation may occur. This adaptation to the size of the mass is readily demonstrated by balloon experiments. No doubt the pressure exerted by the material, in normal people at least, eventually reaches a threshold value and then acts as a stimulus for defecation. The observations of Cowgill and associates[27] suggest that there is a certain capacity of the lower bowel for expansion which accounts for the varying size of the stool; if the amount of material to be eliminated is greater than can be taken care of by this capacity for expansion, then more stools will have to be formed and passed in unit time, and therefore the rate of laxation will be increased.

It is a common belief that defecation at least once a day is a most desirable condition to maintain. It is interesting, therefore, to find Alvarez challenging this view: he points out that he has known many individuals who defecate once every two to four days, and who are apparently in no way harmed by such infrequent evacuation. Although this may be true, it is questionable whether this is sufficient justification for rejecting a more frequent defecation as the ideal to be attained by most people.

The Effects of Foods on Laxation.—Studies of this problem have shown that two types of influences may be exerted on laxation through the medium of foods: (1) one due to the bulk or mass upon which the colonic wall may contract, and (2) another due to the presence of substances which can stimulate the intestine directly by a species of drug action. The first may be illustrated by a comparison of the effects on the time of passage through the entire canal of two diets differing only in their content of indigestible material. If the differences in roughage content are sufficiently great the ration possessing the larger amount will pass through in shorter time and will be passed more easily in the defecatory act. The second type of influence is illustrated in the use of certain foods which seem to increase laxation out of all proportion to the amount of indigestible residue they contain. To what extent these two types of stimuli operate under ordinary conditions is difficult to say. The studies of Cowgill and coworkers[28] suggest, that in normal men at least, there is a definite relationship between rate of laxation and the intake of crude fiber. On the basis of their findings, these authors suggest that an intake of not less than 90 to 100 mg. of crude fiber per kilogram of body weight per day should be associated with satisfactory laxation determined not only by actual amount of material eliminated but by the subjective impressions of the individual as well. Working with a group of men, each of whom presented a history of chronic constipation, it was observed that these patients for some unexplained reason, showed a greater ability to decompose the ingested crude fiber of certain fruits and vegetables than did the normal men: a diet in which the crude fiber was furnished by fruits and vegetables and which gave satisfactory laxation in the normal men, did not do so with these patients; a change to a more resistant type of fiber such as that found in wheat bran, however, gave satisfactory results in both groups. In the one individual whose constipation was of the "irritable colon" type, no form of added roughage was tolerated; even agar-agar in large doses was objectionable, although a small daily dose proved fairly satisfactory. The more recent observations of Williams and Olmsted[126] and others[28, 56] suggest that these differences are probably due to the so-called crude fiber consisting of at least three substances, namely lignin, cellulose and hemicellulose, the presence of these carbohydrates in foods in varying amounts, and the fact that they differ in the extent to which they undergo bacterial decomposition during passage through the alimentary tract, lignin being most resistant and hemicellulose the least.

Ivy and associates[57] have made records of the contractions of the rectum in normal men and in patients suffering from constipation. The patients were found to be much less sensitive to increased pressure in the rectum than the normal individuals. This suggests that chronic constipation may be associated with a marked increase in the threshold for pressure stimulation in the rectum, with the result that the individual fails to respond in normal fashion to the presence of material in the distal colon and rectum ready for evacuation.

Sometimes the surgeon wishes to reduce the defecation rate to a minimum. If an operation is to be performed in the anal region, it is highly advantageous that defecation be delayed for many days, if possible, in order to promote healing and to avoid infection in the operated area. Clinical experience indicates the wisdom of feeding meat to such a patient. Hosoi, Alvarez and Mann[59] made a study of the amount of residue contained in the discharge from the small intestine following ingestion of various foods. Meat was found to have a low-residue value thus confirming the clinical impressions. Students searching for a low-residue diet will find the list of foods tested by Hosoi and associates full of valuable suggestions.

CHAPTER LXV

HUNGER AND APPETITE

The sensations of hunger and appetite are closely related in the sense that both are agencies which promote the taking of food. From the physiological point of view, however, they appear to be due to fundamentally different causes, and it is essential that the two be clearly distinguished. The sensation of hunger has been well described as "a dull ache or gnawing pain referred to the lower midchest region and the epigastrium" (Cannon), and it is definitely correlated with contraction of the stomach. Appetite, on the other hand, is a complex subjective experience compounded of a variety of psychic elements the most important of which are memory impressions of the sight, taste, and smell of palatable food. At present no evidence is available indicating that any specific bodily change underlies the sensation of appetite. Accordingly the following discussion will be concerned chiefly with hunger.

When in common parlance we say that we are "hungry" we usually mean only that we have a good appetite. Among prosperous people with regular habits there are individuals who experience the sensation of hunger only occasionally; in them appetite assures the taking of sufficient food. When, however, in a healthy person the ingestion of food is unduly delayed the more insistent demands of hunger are likely to lead to energetic activities directed toward the satisfaction of the bodily need. The fundamental differences between hunger and appetite have been aptly illustrated by Cannon in his discussion of this subject: "Hunger may be satisfied while the appetite still calls. Who is still hungry when the tempting dessert is served, and yet are there any who refuse it, on the plea that they no longer need it? On the other hand, appetite may be in abeyance while hunger is goading. What ravenous boy is critical of his food? Do we not all know that 'hunger is the best sauce'? Although the two sensations may thus exist separately, they nevertheless have the same function of leading to the intake of food, and they usually appear together. Indeed, the coöperation of hunger and appetite is probably the reason for their being so frequently confused."

HUNGER

In the main two opposed theories have been put forward to explain the sensation of hunger. The first and oldest of these is that hunger results from some general condition of the body, such as a lowering of the content of food substances in the blood. It has been supposed that the reduction in circulating nutritive material, or some change resulting from this, acts upon the brain to produce the sensation. No evidence, however, has been put forward to indicate that any change in the blood is a necessary condition for the development of hunger. As a matter of fact two of the most characteristic features of the sensation, its quick onset and its intermittency, alone suggest that some critical change in the body rather than the slow attainment of a low level of nutrition underlies the subjective experience. In the absence of positive evidence that hunger is a general sensation the older view has given place to the theory that hunger is the result of a specific gastric change.

The first direct proof that hunger is associated with contractions of the stomach was secured by Cannon and Washburn in 1911. The motor phenomena

which they studied were revealed by a technique which has been used in subsequent investigations of hunger (Fig. 345).

Cannon has described the general procedure used in the experiments. Mr. Washburn, at that time a medical student, first accustomed himself to the presence of a rubber tube in the esophagus. When a record was to be taken, a thin-walled rubber balloon fastened on the end of the tube was swallowed. The balloon was then moderately distended with air and connected with a suitable manometer and recording device. Contractions of the fundus of the stomach were thus registered in the usual way on a kymograph. "On the days of observation Washburn would abstain from breakfast, or eat sparingly; and without taking any luncheon would appear in the laboratory about two o'clock. The recording apparatus was arranged as above described. In order to avoid any error that might arise from artificial pressure on the balloon, a pneumograph, fastened below the ribs, was made to record the movements of the abdominal wall. Uniformity of these movements would show that no special contractions of the abdominal muscles were made. Between the records of gastric pressure and abdominal movement, time was marked in minutes, and an electromagnetic signal traced a line which could be altered by pressing a key. All these recording arrangements were out of Washburn's sight; he sat with one hand at the key, ready whenever the sensation of hunger was experienced to make the current which moved the signal." (Cannon.)

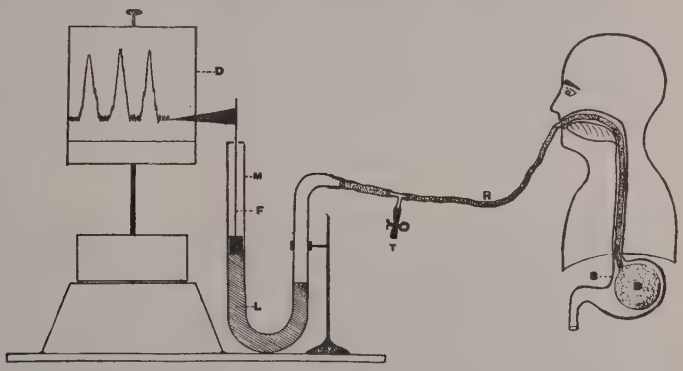


Fig. 345.—Diagram of method for recording stomach movements. *B*, rubber balloon in stomach; *D*, kymograph; *F*, cork float with recording flag; *M*, manometer; *L*, manometer fluid (bromoform, chloroform, or water); *R*, rubber tube connecting balloon with manometer; *S*, stomach; *T*, side tube for inflation of stomach balloon. (From Carlson.)

This relatively simple method at once showed that in man contractions of the stomach occur concomitantly with the pangs of hunger. When hunger was not experienced by the subject, there were no contractions of the empty stomach. Whenever the sensation was felt, powerful contractions of the stomach were recorded. Typically there were periodic recurrences of the sensation and each was associated with a marked rise in intragastric pressure (Fig. 346). It is significant that almost always the contraction was well advanced before the subject recorded the beginning of the sensation. This fact is evidence that the contraction precedes the sensation; indeed it strongly suggests that the contraction is actually the immediate cause of the sensation.

Shortly after this pioneer work the study of hunger was taken up by Carlson of Chicago who made observations on himself and his collaborators as well as on a man with a permanent gastric fistula. Carlson and his collaborators confirmed the evidence brought forward by Cannon and Washburn, and in a long series of studies they have greatly extended our knowledge of the

nature and control of hunger. Much of the material used in this chapter is taken from their published results. The monograph by Carlson should be consulted for further details.

The record obtained when the balloon is placed in the empty stomach of a normal person shows four types of waves. Two of these may be discounted, for they are due to the arterial pulse and the respiratory movements. The third is known as the *tonus rhythm*, and is caused by tonic contractions of the fundus which vary in amplitude (Fig. 347). These changes in tone are not necessarily accompanied by subjective sensations of hunger.

The fourth and most significant type consists of powerful *rhythmic contractions*, alternating with periods of quiescence. These contractions occupy a period of about thirty seconds, and are superimposed upon the tonus rhythm. They gradually increase in amplitude and frequency and, in the case of young and vigorous persons, may pass into a condition of incomplete tetanus, after

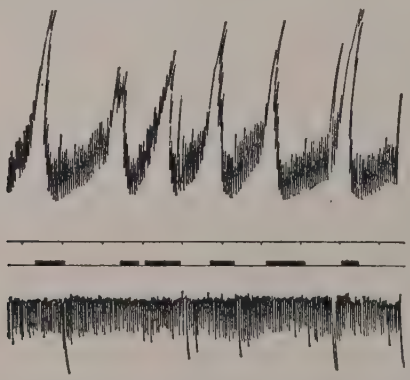


Fig. 346.—Copy of the first record of hunger contractions associated with hunger pangs, made May 17, 1911. First published by Cannon and Washburn, 1912. The top record represents intragastric pressure, the small oscillations being due to respiratory movements, the large to contractions of the stomach; the second record is time in minutes; the third record is Washburn's report of hunger pangs; the lowest record is respiration registered by means of a pneumograph about the abdomen. (From Cannon: Digestion and Health, New York, 1936. W. W. Norton and Company.)

which they suddenly subside, leaving only a faint tonus rhythm. The rhythmic contractions are definitely associated with the sensation of hunger, and are more marked the more intense the sensation is. When tetanus occurs the hunger sensation is continuous, but it instantly disappears when the tetanus gives place to relaxation.

When the contractions are comparatively feeble, the length of the period during which they occur is about twelve minutes. When the contractions are powerful, the periods are always initiated by weaker contractions with long intervening pauses; finally the pauses disappear and the contractions become more and more pronounced until, as mentioned above, a virtual tetanus lasting from two to five minutes, may supervene. The duration of the entire hunger period varies from one-half to one and a half hours, with an average of from thirty to forty-five minutes, and the number of individual contractions in a

period varies from twenty to seventy. Between the hunger periods, intervals of from one-half to two and one-half hours of quiescence may supervene.

Similar contractions, often passing into activity resembling incomplete tetanus in skeletal muscle, have been observed in the stomach of healthy *infants,* some of the observations having been made before the first nursing. The intervals of motor quiescence between the hunger periods are shorter than in adults. In observations made during sleep, it was observed that, when the contractions were very vigorous, the infant would show signs of restlessness and might awake and cry. As in the adult, the contractions are evidently associated

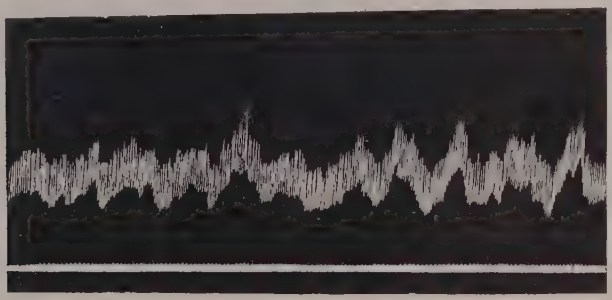


Fig. 347.—Tracing of the tonus rhythm of the stomach (man) three hours after a meal. (From Carlson.)

Fig. 348.—Tracings from the stomach during the culmination of a period of vigorous gastric hunger contractions. One-half original size. (From Carlson.)

with subjective sensations of hunger. Contractions of the empty stomach have also been recorded on a large variety of animals, including the dog, cat, rabbit, guinea pig, bird, frog, and turtle. They vary somewhat in type in different animals.

With regard to the time of onset of the tonus and hunger contractions it has been observed that the only period during which the fundus is free from them is immediately after a large meal. After a moderate meal the tonus rhythm begins to appear in about thirty minutes. It gradually increases in intensity, until by the time the stomach has nearly emptied itself the tonus has become conspicuous, and the stronger hunger contractions usually begin to ap-

pear. Superimposed upon those of the tonus rhythm, hunger pangs may appear in man *when the stomach still contains* traces of food.

By studying the shadow of the outline of the stomach produced by having a person or animal swallow two balloons, one inside the other and with a paste of bismuth subnitrate between them, it has been observed that the weaker type of hunger contraction begins as a constriction involving the cardiac end of the stomach, and moves toward the pyloric end as a rapid peristaltic wave. When the contractions are very vigorous, this wave spreads so rapidly over the stomach that it is difficult to determine whether it really occurs as a very rapid peristalsis or as a general contraction. At the height of the contraction the lower portion of the stomach may become so constricted that the cavity is completely obliterated. These contractions resemble very closely the movements that have sometimes been observed after a bismuth meal of the ordinary type and they have been thought by clinical observers to indicate a hyperperistalsis of the stomach. The digestion contractions of the filled stomach, therefore, pass gradually over into the hunger contractions of the empty organ.

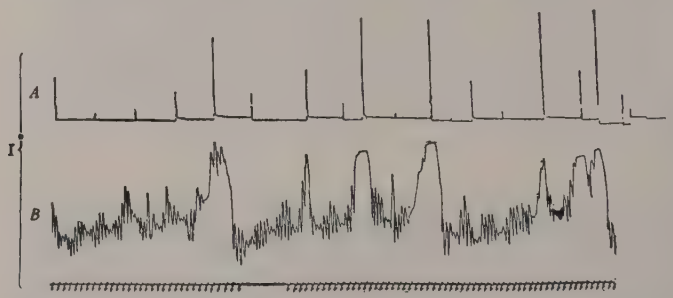


Fig. 349.—Showing augmentation of the knee jerk (upper tracing) during the marked hunger contractions (lower tracing). (From Carlson.)

Remote Effects of Hunger Contractions.—It is well known that during hunger certain general subjective symptoms are likely to be experienced, such as a feeling of weakness and a sense of emptiness, with a tendency to headache and sometimes even nausea in persons who are prone to headache as a result of toxemic conditions. Headache is likely to be more pronounced or perhaps present only in the morning before there is any food in the stomach. These symptoms indicate that hunger contractions are associated with hyperexcitability of the central nervous system, and it is of considerable interest that objective signs of this association can be elicited. If the knee jerk be recorded along with a record of the gastric contractions, it will be found that this reflex shows a marked exaggeration which is simultaneous with the strong hunger contractions of the empty stomach; this augmentation is greatest at the height of the stomach contractions, when the hunger pangs are most intense, and falls off again to normal when these disappear (Fig. 349). Further changes occurring during the hunger period include an increase in the pulse rate and vasodilatation. By comparing plethysmographic tracings of the arm volume with simultaneous records of stomach contractions, it has been found that the increase in volume occurs *pari passu* with the increasing tonus of the stomach, but that shrinking

of the arm begins before the stomach contraction has reached its maximum. Occasionally, however, as in acute hunger, a somewhat different relationship obtains, vasodilatation being more prominent. During each hunger contraction there is also increased salivation, the degree of which varies with different individuals. This response is independent of the more copious "watering of the mouth" that accompanies the thought and sight of appetizing food.

Hunger During Starvation.—During enforced starvation for long periods of time, it is known that healthy individuals at first experience intense sensations of hunger and appetite, which last, however, only for a few days, then become less pronounced and finally almost disappear. It is of interest to know the relationship between these sensations and the hunger contractions in the stomach. This has been investigated by Carlson and Luckhardt, who voluntarily subjected themselves to complete starvation, except for the taking of water, for four days. During a great part of this time records of the stomach contractions were taken by the balloon method, and it was found that the tonus of the stomach and also the frequency and intensity of the hunger contractions became progressively more pronounced as starvation proceeded. Towards the end of the period it was also noted that incomplete hunger tetanus made its appearance where ordinarily, as in Carlson's case, this type of hunger contraction was infrequent. Sensations of hunger were present more or less throughout the period, being therefore probably due to the persistently increased tonus. The onset of a period of hunger contraction could usually be foretold by an increase in the hunger sensation, and as these contractions became more marked, the hunger sensations became more intense. On the last day of starvation a burning sensation referred to the epigastrium was added to that of hunger. The appetite ran practically parallel with the sensation of hunger, and both of these sensations became perceptibly diminished on the fourth or last day of starvation, this diminution being, however, most marked in the sensation of appetite. Indeed, instead of an eagerness for food, there developed on the last day a distinct repugnance or indifference towards it. Accompanying these sensations of hunger and appetite a distinct mental depression and a feeling of weakness were experienced during the latter part of the starvation period.

On partaking of food again the hunger and appetite sensations very rapidly disappeared and also practically all of the mental depression and a great part of the weakness. Complete recovery from the latter, however, did not take place until the second or third day after breaking the fast. From this time on both men felt unusually well; indeed they state that their sense of well-being and clearness of mind and their sense of good health and vigor were as greatly improved as they would have been by a month's vacation in the mountains. They further point out that, since others who have starved for longer periods of time unanimously attest to the fact that, after the first few days, the sensations of hunger become less pronounced and finally almost disappear, they must have experienced the most distressing period during their four days of starvation. Although the hunger sensation was strong enough to cause some discomfort, it could by no means be called marked pain or suffering, and was at no time of sufficient intensity to interfere seriously with work. Mere starvation cannot therefore be designated as acute suffering. It is of further interest to note that during the starvation period a continuous flow of acid

gastric juice was found to be occurring in the stomach, to the presence of which the burning sensation experienced in the epigastrium on the last days is probably to be attributed.

Control of the Hunger Mechanism.—Carlson showed that hunger contractions of the empty stomach occur after complete isolation from the brain and spinal cord but at longer intervals and with less vigor than in normal animals. This suggests that chemical changes in the blood acting directly on the stomach may be responsible for them. It is of significance in this connection that when the blood sugar level is lowered by about 25 per cent, as by the use of insulin, hunger contractions become very marked, to disappear promptly when the lack of sugar in the blood is met by injection of the carbohydrate. The contractions are more vigorous when the innervation is intact. These experimental observations serve to explain the pronounced hunger sensations experienced by individuals who have received too much insulin.

Variations and Inhibitions of the Hunger Contractions.—The stimuli that may set up efferent impulses traveling by the extrinsic nerves to the stomach are impulses in sensory nerves or are of psychic origin. Stimulation of the gustatory end organs in the mouth, as by chewing palatable food, always causes an inhibition of gastric tonus and a diminution or disappearance of the hunger contractions. Even the chewing of indifferent substances, such as paraffin, suffices to produce distinct inhibition, unless the contraction has passed into a tetanus. It is of interest that swallowing movements, in the absence of any food substance in the mouth, are sufficient to produce a transitory inhibition of the gastric tonus—a receptive relaxation of the stomach, as it has been aptly called. The diminution in tonus and hunger contractions brought about in these various ways is accompanied by a diminution in the hunger pains.

Afferent nerve stimulation affecting the hunger contractions may also originate in the *gastric mucosa itself,* as was shown by Carlson when he introduced various substances to be tested through a tube into the stomach of his patient (Mr. V.). A glassful of cold water given in this way inhibits the tonus and the hunger contractions, unless these are severe, for from three to five minutes; this inhibition is not followed by any augmentation either of the tonus or of the contractions. Ice-cold water has a greater effect than water at body temperature.

Weak acids of strengths varying up to that found present in the gastric juice itself—0.5 per cent—cause a marked inhibition of the hunger movements, but this inhibition does not persist until all the acid has either escaped from the stomach or been neutralized, a fact which explains why hunger contractions may still occur when an acid secretion is present in the stomach, as in starvation. Normal gastric juice itself produces an inhibition, which is no doubt dependent upon the acid which it contains, but there is no basis for the view that, at the same time that it leads to inhibition of the hunger contractions, the acid initiates peristalsis of the pyloric region. Weak alkaline solutions have no greater effect on the hunger contractions than an equal volume of water. Weak solutions of local anesthetics, such as phenol or chloretone, are without effect.

With regard to *alcoholic beverages* interesting results were obtained. Wine, beer, brandy, and diluted pure alcohol inhibit both the tonus and the contractions. The duration of this inhibition varies directly with the quantity of the beverage introduced into the stomach and with its alcohol percentage. These

observations are apparently not in harmony with the experience of most men that the taking of alcoholic beverages serves to awaken or increase the appetite, the difference being no doubt due to the fact that hunger contractions of the stomach and appetite are not dependent on one another. As we have already seen, appetite is a complex psychic affair, whereas the hunger contractions and the sensations they arouse depend upon a local mechanism in the stomach wall itself.

The hunger contractions may be inhibited by the presence in the intestines of different substances, for example, carbohydrates, milk, oil, water, alkalies, and gastric juice. The mechanism by which this type of inhibition is brought about has been studied recently by Quigley and Phelps,[104] who placed carbohydrate in the intestines of dogs provided with a completely denervated isolated stomach or a completely denervated auto-transplanted gastric pouch. It was concluded that the inhibition of the motility of the empty pouches must involve a depressant humoral factor or chalone; a nervous factor may normally be involved because inhibition of the contractions of the normal stomach is produced by less carbohydrate, has a shorter latent period and lasts longer, but these differences may indicate merely a reduced susceptibility of the denervated tissue to the humoral factor. Action of this humoral factor depends on the presence of the carbohydrate in the upper intestine but not in the stomach itself.

Various other inhibitory factors have been discovered. Smoking has this effect, and compression of the abdomen by tightening the belt also inhibits the contractions, provided they are not of marked intensity. Considerable muscular exercise, such as brisk walking or running, causes an inhibition, which usually persists until the exercise is discontinued. When the tonus and the contractions return after exercise, they seem to be somewhat more pronounced. Application of cold to the surface of the body causes an inhibition of the gastric tonus and hunger contractions, the degree of which is roughly proportional to the intensity of the stimulation. If such stimulation is maintained, the inhibitory effects on the stomach gradually diminish, even though the individual be shivering intensely; there is never an increase in the gastric tonus and the hunger contractions.

With regard to *the nerve centers concerned in these phenomena,* little that is definite is known. The sensory nuclei of the vagus nerve in the medulla must be considered as the primary hunger center, and through this center, not only influences affecting the stomach contractions, but also those associated with the hunger sensations, must be mediated. It would appear from observations on the hunger behavior of decorticate animals that there can be no absolutely essential hunger center located in the cerebral cortex itself, for such animals exhibit practically the same hunger effects as normal animals. It is interesting to note that, at least in the case of "decorticate" pigeons, this hunger behavior entirely disappears on removal of the optic thalami. It appears therefore that important nerve centers having to do with the bodily responses of the animal to hunger impulses are located in the brain stem, presumably in the diencephalon.

Concerning the influence of psychic states, Carlson says that in his own case the hunger contractions became weaker and the interval between them greater when he was suddenly awakened during his fast and saw two of his friends partaking at his bedside of a "feast of porterhouse steak with onions, potatoes,

and a tomato salad." These results are no doubt due to local inhibition dependent upon the psychic secretion of appetite gastric juice. When no such juice is produced, the sight and smell of good food do not appear to affect materially the hunger contractions of the stomach. No doubt they stimulate the appetite, but that, as we have seen, is a psychic affair.

In the diagnosis of gastric and duodenal ulcer stress has been laid upon the occurrence, two to three hours after a meal, of pains which are relieved by the ingestion of food. The pains are probably due to hunger contractions. They can often be relieved by administration of alkalies of which the most useful for repeated use is a mixture of sodium bicarbonate, calcium carbonate, and magnesium carbonate. This has the advantage over sodium bicarbonate alone in that it causes less disturbance of the acid-base equilibrium of the organism. The alkali acts by neutralizing the excess of acid which is contained in the gastric secretion in cases of duodenal ulcer. Another type of treatment is to give olive oil. This acts by its inhibiting effect on gastric secretion (see page 911).

CHAPTER LXVI

THE BIOCHEMICAL PROCESSES OF DIGESTION

In a book on physiology, as distinct from a treatise on biochemistry, it would be out of place to enter into details concerning the chemical processes taking place during the digestive process. There is, however, a certain amount of fundamental knowledge which it is essential that we should consider. In the first place, it should be borne in mind that in the digestion of carbohydrates and proteins, various intermediate stages are passed through before the final absorption products are formed. The highly complex molecule of which protein, for example, is composed, is first of all broken down into several smaller but still highly complex molecules, each of which then undergoes further disruption, until ultimately the amino acids or relatively simple combinations of them are set free. Certain enzymes, such as trypsin, can carry this process from the beginning through the greater part of its course without the assistance of other enzymes, but in the natural process of digestion, as it occurs in the gastrointestinal tract, the different stages of the disruption are brought about successively by different enzymes. One enzyme prepares the food for the action of the next. This interdependence of their actions demands that some provision should be made whereby each enzyme is secreted at the proper time; that is, when the foodstuff has already been prepared for its action by that of its predecessor. Thus, it would be useless after food is taken for the gastric and pancreatic juices to be secreted at the same time. Instead, the gastric juice is secreted first and the pancreatic only after the food has been prepared for its action. This correlation in function we have already seen to be dependent largely on the action of hormones.

SALIVARY DIGESTION

The biochemical processes of digestion in man begin with the action of saliva. The most important constituents of the saliva are the amylolytic enzyme *ptyalin* and *mucus*. The amounts of these substances are subject to some variation. Some individuals, otherwise normal, show very little ptyalin in their saliva, in contrast to others whose saliva possesses considerable digestive power. Therefore one cannot consider a measurement of salivary activity as any index of serious abnormality. The saliva of certain species, the dog, for example, is devoid of ptyalin. The dog must rely on the amylase in his pancreatic juice to digest any swallowed starch, and this may be the reason why dogs exhibit increased laxation when forced to subsist on diets high in starch content. The saliva of the rat has great amylolytic power enabling this species to thrive on starch-rich rations. The mucus present in saliva plays an important rôle in lubricating the swallowed bolus.

In the saliva of healthy persons are also found traces of various nitrogenous metabolites—urea, uric acid, etc.—that occur in the blood. The amounts of these substances have been found to vary, the variations reflecting to a considerable degree the concentration changes in the blood. In nephritis, for example, when urea and other metabolites fail to be eliminated sufficiently through the

kidneys and therefore increase in the blood, they increase in the saliva. These facts suggest that chemical analysis of the saliva for these metabolites might perhaps be substituted for blood analyses in diagnostic work, but careful tests of this possibility have revealed that the blood analyses are much more significant. The fact that the saliva may contain relatively large amounts of nonprotein nitrogenous constituents of the blood is of practical clinical value in that the salivary glands may be made to function as one channel of excretion of such substances in case of kidney stress.

Oral administration of sodium iodide soon results in the passage of iodide from the blood into the saliva. This, together with the fact that iodide is not absorbed in the stomach and must therefore pass into the intestine before it can reach the blood, constitutes the physiological basis for the very simple iodide gastric-motor-function test. By timing the appearance of iodide in the saliva following the ingestion of a small capsule of the drug (0.2 Gm.), the time required for the passage of the iodide through the stomach is roughly determined. In cases of iodism considerable iodide is found in the saliva.

Factors influencing salivary digestion are: (1) the amount of ptyalin contained in the saliva, (2) the thoroughness with which the saliva is mixed with the food, and (3) the time during which the enzyme is allowed to act. The result of the action of ptyalin is to split digestible starch to yield the disaccharide maltose. The term "digestible starch" is used here because it has been shown that not all substances classified as starch by the organic chemist are acted upon by the various starch-splitting enzymes in the animal body. Cooked starch is much more readily digested than raw starch. The common idea that raw starch is absolutely indigestible has been shown to be erroneous; there seems to be some relation between the size of the starch granule and its susceptibility to amylase activity, the small granules being much more readily digested than the large granules. This may, perhaps, be due to the fact that the smaller granule has relatively much more surface to present to the enzyme than the large granule. Cooking in all probability acts to rupture the starch grains breaking the hemicellulose cell wall and thus facilitating the contact of the starch with the enzyme.

Reference has already been made to the belief of certain faddists that food should be chewed for long periods in order to "get the most nourishment out of it." There is little doubt that this extensive chewing would result in more complete digestion of the starchy portion of the food. As has already been pointed out, however (see page 921), salivary digestion can proceed for a considerable period in the stomach before the ptyalin is inactivated by the acid gastric juice, and this constitutes a serious argument against the position of these faddists.

Saliva is usually faintly alkaline in reaction. Variations from this have been believed by certain students to be related in some way to the problem of dental caries, particularly when combined with the action of acidophilic bacteria in the mouth. It has also been supposed that the drinking of acid wines and similar fluids at meal time may be detrimental to the action of ptyalin because the optimal reaction for the enzyme is very close to neutrality (pH 6.8). Actual experiment, however, indicates that the ability of common foods and drinks to impair salivary digestion beyond that to be expected by mere dilution of the saliva, may be questioned.

The maltose, which results from the action of ptyalin on starch, is split to yield glucose by the action of a maltase found in the intestinal juice, and the glucose is then absorbed through the intestinal wall.

DIGESTION IN THE STOMACH

The gastric juice contains several important digestive agents: (1) the enzyme pepsin, (2) hydrochloric acid which cooperates with pepsin in its digestive activity, (3) gastric rennin which clots milk, and (4) gastric lipase. The pepsin and the hydrochloric acid are undoubtedly the most important of these substances; they are found particularly in the juice secreted in the cardiac end of the stomach; toward the pyloric end the hydrochloric acid entirely disappears and the pepsin content becomes distinctly less.

The Functions of Hydrochloric Acid.—The functions of hydrochloric acid may be conveniently divided into physiological and biochemical. The former come into play after the chyme has entered the duodenum, and they have to do with the secretion of pancreatic juice and bile through the secretin mechanism (see page 895). The biochemical functions are: (1) assisting the pepsin in the digestion of proteins, (2) bringing about a certain degree of splitting of disaccharides, and (3) exerting an antiseptic action on the stomach contents. Regarding the last mentioned of these functions, it may be said that the chyme of a normal person, as it is ejected from the stomach, is practically but not absolutely sterile; bacterial counts reveal that organisms are present but in very small numbers; the chyme may also contain spores and certain bacteria that are more or less protected against the digestive agents of the stomach. This protection is afforded by an outer covering of a chitinous nature (spores) or, as in the case of the tubercle bacillus, by a covering of waxlike material. It is believed that persons with strictly normal digestion are much less liable to infection by such bacteria as those of typhoid and cholera than persons with less active gastric secretion. When the acid of the gastric juice falls below the level at which it possesses an antiseptic action, various bacteria and yeasts grow in the stomach contents, producing by the resulting fermentation irritating organic acids and gases. It is under these conditions that yeasts, sarcinae, and lactic and butyric acid bacilli find in the gastric contents a suitable nidus on which to grow.

The Amount of Acid (Gastric Analysis).—It has long been known that considerable variations in the amount of hydrochloric acid in the gastric juice may occur not only in disease of the stomach itself but also in general diseases, such as certain forms of anemia. On this account, a more or less elaborate technique has been developed for the purpose of determining the degree of acidity and the concentrations of hydrochloric acid and chlorides in the gastric contents.

The Fractional Test Meal and Related Techniques

The first step in this procedure consists in passing down the esophagus a tube of narrow bore (Rehfuss or Ryle tube), provided at its end with an oval tip in which are wide slots. The tube is so narrow that it can be left in position for several hours without discomfort. It is passed in the morning before any food has been taken; and by means of a syringe attached to the outer end, the residuum of the stomach contents is removed by aspiration. The volume obtained should not amount to more than 50 ml. One pint of thin oatmeal gruel, or of water, is then swallowed, and samples of 5 or 6 ml. each are subsequently removed

at intervals of fifteen minutes during a period of one or two hours. After aspirating each sample, a little air is blown down the tube so that what is left in it may be returned to the stomach. The amount remaining in the stomach after the period of observation is aspirated as a whole. The residuum, each of the samples, and the remainder are then examined for free acidity (free HCl), total acidity, total chlorides, and peptic strength. The older methods employed test meals of different kinds. The newer techniques make use of the drug histamine which has been found to be a potent gastric secretagogue, acting particularly on the acid secreting mechanism. When histamine is used, the drug is injected after the stomach tube has been swallowed and the contents of the resting stomach removed. Some clinicians favor the use of a dilute alcohol test meal. It would be out of place to describe the analytical methods in detail here, but the general principles are as follows:

Free Acidity.—This is due to hydrochloric acid which is not combined with protein. It is determined by titration with standard alkali in the presence of an indicator which changes color at the pH at which the HCl-protein compounds begin to dissociate. This titration value is therefore proportional to the pH of the solution as determined electrically or colorimetrically. The most convenient method is to titrate a measured sample of the fluid (2 ml.), to which a drop of Töpfer's indicator (methyl yellow) has been added, with 0.1 N NaOH until the pink color gives place to an orange one. This change occurs at a pH of about 3.6, and the results are expressed as the number of milliliters of 0.1 N NaOH required to neutralize 100 ml. of the stomach contents (i.e., multiply the milliliters of NaOH used by 50). When a gruel not containing protein is used as the test meal, this method is as accurate as need be for practical purposes, but when protein is present, the results may be too high because some of the protein-HCl compound becomes dissociated near the end point.

Total Acidity.—A drop of phenolphthalein solution is added to the above solution and titration with 0.1 N NaOH is continued until a pink color develops. Normally, only about 10 ml. per 100 ml. of stomach contents is required.

Total Chlorides.—The above fluid is mixed in a small evaporating dish with 5 ml. of HNO_3 (conc.) and 5 ml. 0.1 N $AgNO_3$ solution. After standing a few minutes, so that the precipitate of AgCl may settle, some powdered iron alum is added and the amount of free silver remaining in the solution is determined by titrating with 0.1 N thiocyanate. A pink color develops when all free silver has been precipitated by the thiocyanate. By subtracting the milliliters of thiocyanate used from 5 ml., we obtain the milliliters of 0.1 N $AgNO_3$ which has combined with the chlorides, and since 2 ml. of the stomach contents were used, this multiplied by 50 gives us the milliliters of 0.1 N chloride in 100 ml. This value multiplied by 0.00365 (the molecular weight of HCl) gives us the grams HCl per cent of stomach contents.

Mineral or Neutral Chlorides.—The above procedure is repeated on another sample of stomach contents after it has been evaporated to dryness and incinerated. The incineration drives off the HCl which is not combined with inorganic bases. By subtracting the mineral or neutral chloride from the total chloride, the amount of HCl combined with protein is obtained.

Peptic Strength.—Probably the method most commonly used is that of Mett. Egg white is drawn up into narrow glass tubes and coagulated by heat. A piece of the tubing is then incubated with the gastric contents and the length of the column of egg white which has become digested is measured. It is considered that the length of the column digested is proportional to the square root of the peptic strength. A newer and much more delicate technique is that perfected by Gilman and Cowgill[46] based on the digestion of the protein emulsion of an exposed x-ray film and measurement of the transmissibility of light by the film before and after the digestion.

In normal juice the total acidity steadily rises during the first hour until it reaches about 60 ml. N/10 acid per 100 ml. of juice. It then falls off and is back to 20 or less in a little over two hours. The free acidity is lower and is usually about 20 ml. less than the total in one hour, approaching closer to it in the later fractions. The pH is subject to some variations depending upon the conditions under which the juice is collected, whether the secretion of mucus is stimulated, how much saliva is swallowed and intestinal contents are regurgitated. A rather common finding is a pH of about 1.6-1.8.

When gastric juice is collected through a fistula from an empty stomach, or following histamine injection, or when a nonprotein test meal is given, very

little difference will be found between the free hydrochloric acid and the total acid; that is, between the results obtained by the second and the first of the methods described above. This is because in such juice there is little or no organic matter capable of combining with the hydrochloric acid, mucus being about the only such substance available, and there are no other acids, such as lactic or butyric, which might be produced by fermentative processes. The difference between the two titrations, however, becomes marked when protein food is undergoing digestion in the stomach.

The pathological condition in which there is most definitely a diminution of the hydrochloric acid is cancer, either of the stomach itself or, occasionally, of some other part of the body. In this disease there is invariably an appreciable amount of lactic acid, and some clinicians have gone so far as to claim that every case which yields no evidence of ability to secrete hydrochloric acid but does show lactic acid in the gastric contents is a case of cancer. Histamine has been shown to be of particular value in detecting only a slight ability to secrete hydrochloric acid, and therefore is useful when dealing with borderline and doubtful cases. As already indicated, the presence of lactic acid in the gastric contents has been considered as diagnostic of cancer by certain observers, the acid being considered as the product of a "deranged metabolism" of the cancer cells, but the work of Robertson, described in his monograph (1931), has demonstrated conclusively that this lactic acid is not the dextrorotatory variety found in muscle tissue but the inactive form produced by fermentative processes; by washing out the stomach thoroughly, no further lactic acid is produced until a period sufficient for the development of fermentation has elapsed. In pernicious anemia there is also a marked decrease in gastric acidity. In cases of gastric and duodenal ulcer there is usually a considerable increase.

In this connection it is pertinent to call attention to the common use by clinicians of the term *hyperacidity* to describe conditions characterized by unusually high acidity of the gastric contents. To the extent that the term is taken to mean that the gastric juice elaborated by the glands has a higher concentration of acid than normal, its use is most incorrect. Hollander and Cowgill[58] have shown that hydrochloric acid is normally formed by the cells at a remarkably constant and low pH, this being 0.90 (± 0.01). Therefore, there is no such thing as hyperacidity in the sense that the glands produce a secretion of abnormally high acidity. Carlson has suggested that the term *hypersecretion* more accurately describes the situation facing the clinician. The more or less continuous secretion of acid gastric juice without the usual neutralization of it should result in the finding that the gastric contents were always highly acidic. Excessive stimulation of the gastric glands through humoral factors, particularly those operating during the intestinal phase of gastric secretion (see page 910) could be in part responsible for this condition. The presence of acid in the upper intestine has been shown to stimulate gastric secretion. Discharge of gastric acid chyme into the duodenum together with failure of neutralization processes to function, could therefore operate to promote further secretion of gastric juice. Exclusion from the intestine of the alkaline pancreatic juice could result, theoretically therefore, in gastric hypersecretion. Fauley and Ivy[38] have tested this hypothesis in dogs with a Pavlov miniature stomach and found that such a hypersecretion does occur.

The Source of the Acid.—A question that has puzzled physiologists for many years concerns *the mechanism by which hydrochloric acid is secreted.* The percentage of hydrochloric acid in the gastric juice is considerably above that at which many living organisms can live (a fact demonstrated in part by the antiseptic action of the gastric juice) and yet this acid is secreted by the lining membrane of the stomach. How then do the cells of the gastric glands bring about the separation of this powerful acid from the perfectly neutral blood plasma? In the first place, it is significant that the mucous membrane of the stomach contains a higher percentage of chlorine than the average of other organs and tissues, indicating that it has the power of abstracting chlorine from the blood. The excess of chlorine in the mucosa must, moreover, be but a very small fraction of that actually secreted into the gastric juice. The chlorine content of the mucosa of the cardiac end is considerably greater than that of the pyloric portion of the stomach. These facts indicate that chlorine is attracted by the gastric cells, but they throw no light on the question as to where the hydrochloric acid is really formed.

It is quite well established that the hydrochloric acid is formed by the *parietal cells,* but the process by which these cells produce the acid and the question whether this is formed within the cell or by some chemical reaction in the lumen of the gland are unsolved problems. It has been argued that the latter process must occur, for otherwise the parietal cell would be destroyed by the strong acid. Against this view one may cite the studies of Dragstedt[32] showing that the gastric mucosa is not the only tissue capable of withstanding such high concentrations of acid. Dragstedt sutured various organs into incisions in the stomach wall and so exposed them to the acid secretion of the stomach. Such transplants of kidney, spleen, and other organs were found to be in a healthy state many months later, provided their normal blood supply had not been impaired by the operation; necrotic tissue was very quickly attacked by the acid. These observations should be of interest to the clinician because they show that the gastric acid is not per se a primary cause of ulcer.

The earlier work on this problem consisted of attempts to determine the locus of acid formation by microchemical precipitation of chlorine in the cells, by the staining reactions of the cells and by the formation of Prussian blue following the injection of potassium ferrocyanide and a ferric salt. All of the studies based on these methods have supported the view that the parietal cell is the cell of importance in the process, but that the final formation of the acid takes place in the gland lumen and not within the cell itself. The more recent work of Gilman and Cowgill,[48] suggesting that the concentration of the hydrochloric acid is dependent in considerable measure on the osmotic concentration of the blood, affords some support for another hypothesis. This postulates that the parietal cell secretes the acid as such but in very dilute concentration. As this secretion passes down the glandular lumen, water is actively absorbed by the gland cells as, for example, in the kidney tubule, but the mucosa cells are impermeable to the acid. This results in a gradual concentration of the acid, a process which can proceed, theoretically, until osmotic equilibrium with the blood is reached. Such a theory harmonizes well with the results of previous studies and does not seem to involve any wholly untenable assumptions. The reader will notice, however, that even this hypothesis does not completely explain the origin of the acid

within the cell. This might conceivably be due to certain peculiar properties of the membrane of the parietal cell permitting the transfer of both hydrogen and chlorine in ionic form.

Acid Responses in Human Beings.—In the average normal human subject a plot of total and free acid against time, following administration of the test meal or histamine stimulus, gives a curve characterized by a definite rise culminating in a peak or plateau and then a rather rapid fall. Maclean calls this type of curve an *isosecretory curve*. Some investigators hold that the curve for concentration of free acid gives just as much information of diagnostic value as that based on the total acid. In cases of so-called hypersecretion, the free acid continues to increase throughout the period of the test, often becoming as much as twice the maximum value commonly yielded by the normal subject. In hyposecretion the concentration of free acid remains low during the test or, if it increases at all, reaches a maximum that is far below that obtained in normal individuals. When endeavoring to interpret any given responses the student will do well to exercise some caution and to remember Carlson's statement that he has seen all of the supposedly significant curves obtained in clinical work duplicated in his laboratory in experiments on perfectly normal people. It should also be borne in mind that the various curves do not truly represent the actual amounts of acid secreted. To date no method has been devised that accomplishes this. During the period of the test, material has been discharging through the pylorus, and the amount discharged is undetermined. Furthermore, part of the acid in all probability is being constantly neutralized by regurgitation of alkaline fluid from the intestines. The extent of such neutralization can be estimated roughly by determining the amount of total chlorides in the gastric contents.

The phenomenon of maximum acidity has led to the suggestion that the stomach regulates the acidity by pouring out when necessary what has been called a neutralizing secretion in which the chlorine is present in the form of a neutral compound. The work of Maclean and Griffiths offered in support of this view has had extensive reexamination recently, chiefly in the studies of Wilhelmj and associates,[125] and those of Apperly and co-workers,[4] and is not confirmed; evidence is offered showing that regurgitation of alkaline material from the duodenum is the chief factor in regulating the acidity of the gastric contents.

The digestive action of hydrochloric acid is closely linked with that of pepsin, with which it will, therefore, be considered.

The Action of Pepsin.—A pepsin may be defined as a proteolytic enzyme which acts best in an acid medium. The pepsin of the gastric juice acts in conjunction with the hydrochloric acid. The enzyme is probably secreted by the chief cells of the gastric glands. Microscopic studies of the cells suggest that they elaborate pepsin in an inactive or precursor form called pepsinogen. Studies of extracts of the gastric mucosa also support this view. A water or glycerin extract of the tissue is not affected by treatment with alkali, whereas similar treatment of an acid extract results in a loss of digestive power. There is some evidence for the view that in nature there are different pepsins. Pepsin of the dog, for example, acts best in a hydrogen ion concentration corresponding to that of a 0.05 N. hydrochloric acid solution, whereas that of the human stomach works best at a concentration of 0.03 N. There are also certain differences with respect to the optimum temperature at which they act, and with regard

to the nature of the protein which they attack most readily. Although pepsin requires the presence of acid, this action of acid does not appear to depend solely on the hydrogen ion concentration; the other ion in the acid may play a rôle. For example, hydrochloric acid is much more effective than sulfuric acid, the SO_4 ion seeming to be unfavorable for some reason. There is evidence that the acid combines with the protein before the pepsin attacks the latter; for, if we first combine the protein with acid and then wash away all traces of free acid, the protein can be digested in a neutral pepsin solution without the liberation of any free acid. It has also been found that the pepsin becomes combined with the protein in the proteolytic process, for if elastin or fibrin is first immersed in a pepsin solution and then taken out and washed thoroughly to get rid of adherent pepsin, it will be found, on placing it in a hydrochloric acid solution of the proper strength, that peptic digestion proceeds. By means of such a method it has been possible to show that pepsin is present in intestinal contents and not immediately destroyed by trypsin of the pancreatic juice, as was formerly supposed.

Both pepsin and its precursor pepsinogen have now been isolated by Northrop and demonstrated to be protein in nature. Pepsins prepared from bovine gastric juice and pig gastric extracts in general show similar properties but can be distinguished by solubility measurements. "It is probable, therefore, that the various pepsins differ from species to species, as do the hemoglobins" (Northrop[98]). It is well for the student to bear in mind that crystalline pepsin differs from the crude preparations ordinarily used in digestion experiments in that the latter also contain another enzyme, gelatinase, which liquefies gelatin, and many so-called tests for pepsin really measure the activity of this gelatinase instead of the true pepsin.

Products of Peptic Digestion.—Pepsin does not completely disintegrate protein; it merely forms certain large molecular fragments which are still protein and quite complicated in nature. The first product is a metaprotein known as acid albumin or syntonin. This may be precipitated from the digest by careful neutralization of the acid. The next product is known as primary proteose; it is precipitated by half saturation with ammonium sulfate. The third product is secondary proteose, separated by complete saturation with ammonium sulfate. After all of these substances have been removed, there still remains in solution the fourth product—peptone—which, among other things, is characterized by the fact that with the biuret test it gives not a violet but a rose-pink color. It is important to note that the term *proteose* is a general one, and that it signifies in all probability a group of protein bodies falling within a certain range of molecular size, the molecules, however, being large enough to be salted out by increasing concentration of ammonium sulfate and other salts. Likewise, *peptones* constitute a group of proteins produced in the digestion, and characterized by another range of still smaller molecular size; in this case the molecules are too small to permit their removal by the salting-out process. Most of the commercial peptones are not pure preparations but merely mixtures of all of the soluble products of peptic digestion. This fact is not always appreciated by bacteriologists who use the commercial products in their experiments and erroneously refer their findings to true peptones. Along with the proteoses and peptones, a certain amount of free amino acids may also appear in peptic digestion. These facts, considered together with the observation that pepsin fails to digest the

largest synthetic polypeptide thus far prepared by the organic chemist, support the view that pepsin does not act primarily on peptide linkage but upon other types of chemical union existing in protein.

Under certain conditions the action of pepsin can be reversed so that proteoses and peptones are resynthesized into protein. This resynthesized protein has been called plastein,[119] it coagulates on heating and gives a biuret test like that of native proteins. Such a synthesis is theoretically possible if our current conceptions of the nature of enzyme action are correct, and the achievement of this synthesis therefore constitutes an interesting confirmation of these theories of enzyme activity.

Most, but not all, of the pepsin which leaves the stomach is destroyed in the intestine. A part of it may be absorbed into the blood and carried back to the gastric glands to be used again. This would account for the presence of antipepsin in the blood, and also for the presence of pepsin in the urine.

Clotting of Milk in the Stomach; Gastric Rennin.—Gastric juice has the power of clotting milk. Formerly it was supposed that this was due to pepsin, and it is true that all pepsins thus far tested have been shown to possess this property. It is also true that the acid alone will clot milk although study of the chemical changes undergone in the clotting indicates that the action of the acid is different from that of the enzyme. Hammarsten obtained evidence supporting the view that there is another enzyme besides pepsin in gastric juice endowed with the specific property of clotting milk. This precipitated a long controversy which seems to have been settled in favor of Hammarsten's theory. The enzyme is called *rennin*. During the clotting process rennin acts on the protein casein, splitting it to yield paracasein and whey albumose; the former, in the presence of calcium ions, is precipitated as a calcium compound. The prolonged controversy over the question of the identity of pepsin and rennin seems to have been caused by the fact that pepsin, although powerfully proteolytic, can clot milk to some extent, whereas rennin is extremely active in clotting milk but does show some slight proteolytic activity. The significance of gastric rennin is difficult to state. It has been argued that it is a decided advantage to the young nursing mammal to have the protein material of milk precipitated in the stomach; unfortunately, this fails to explain why rennin is present in the gastric juice of all vertebrates from the fishes to the primates. Bradley[15] suggests that both rennin and pepsin are parts of one large complicated enzyme complex, which undergoes a characteristic development, and in this way endeavors to explain the greater abundance of rennin over pepsin in the stomach of the young animal as compared with the adult. It is, of course, quite possible that rennin has some other as yet entirely unknown function; isolation of the enzyme in pure state and extensive studies of its properties would doubtless throw much light on this interesting possibility.

Other Digestive Changes in the Stomach.—

Gastric Lipase.—The gastric juice contains an enzyme which acts on fats, namely, gastric lipase. It is not very effective on such fats as olive oil, but on fats that are highly emulsified it is very active. The results of its action are the production of glycerol and fatty acids.

Intrinsic Anemic Factor.—In his studies of pernicious anemia Castle has been able to show that the normal stomach is able to produce some change in

meat (muscle) which gives it therapeutic value in the treatment of this disease; the stomach of the pernicious anemia patient is unable to bring about this change. In spite of much research on this question Castle and his associates have as yet been unable to relate this "intrinsic" biologic factor in gastric digestion to any of the known digestive agents. The discovery of its true nature therefore remains as one of the important objectives of future research.

DIGESTION IN THE INTESTINES

The further changes which the half-digested foodstuffs in the chyme undergo in the intestinal canal depend on the enzymes present in the secretion of the various glands and on the presence of bacteria. The most important of these secretions are the pancreatic and intestinal juices and the bile. The latter does not contain any enzyme, and in this sense is not a digestive juice; its influence on digestion is very great, however, because its constituents, the bile salts, greatly facilitate the action of pancreatic lipase as well as aid in the absorption of fats.

Pancreatic Digestion

The chief enzymes of the pancreatic juice are trypsin, lipase and amylase; erepsin is also present. The pH of the juice is over 8.5 and its titrable alkali about equals that of the acid of the gastric juice (about 0.1 N).

The Action of Trypsin.*—When the pancreatic juice enters the duodenum, it immediately develops powerful proteolytic powers, and this occurs also when "secretin juice" from the duct of the gland is mixed with an extract of the mucous membrane of the duodenum. This is due to the activation of trypsinogen to trypsin. A very small amount of the extract is capable of increasing the digestive activity of a very considerable quantity of pancreatic juice, and this property of activation is readily destroyed by heating the extract, showing that the action depends on the presence of an enzyme which has been called *enterokinase.*

On account of the large quantities of alkali in the pancreatic juice and bile, the acidity of the chyme is practically neutralized in the upper reaches of the intestine. A little lower down, however, an acid reaction may again develop. It is interesting to note that as a result of the great secretion of alkali by the pancreas, extracts of this organ after death show a very high degree of acidity in comparison with extracts from other organs and tissues. The activity of trypsin does not depend on the presence of free hydroxyl ions, as was previously supposed, but it may proceed in the presence of a decided amount of free acid. If pepsin is present together with trypsin in a distinctly acid solution, the pepsin seems to destroy the trypsin, unless the mixture contains a considerable quantity of protein, when the tryptic activity may persist even for several hours. Studies have also revealed the presence of trypsin in the stomach as a result of regurgitation of intestinal contents through the pylorus. A practical conclusion which we may draw from these results is that preparations of trypsin—the so-called *pancreatin,* for example—if given with the food, may pass in an active condition into the duodenum, where, in the

*It will be advantageous for the reader at this stage to review the chemical structure of proteins, fats, and carbohydrates, as outlined in the chapters on metabolism.

more favorable environment created by the neutralization of the excess of acid, it will develop its proteolytic power. The therapeutic administration of pancreatin is, therefore, justified (Long[76]).

Activated trypsin acts on proteins by breaking down many of the peptide linkages. The enzyme, therefore, acts in a different manner from pepsin. Thus, after tryptic digestion has proceeded for some time, only a trace of primary proteoses, but considerable quantities of leucine, tryosine, and other amino acids will be found present, although a good many peptide (NH-CO) linkages are still left unbroken, indicating that certain polypeptides are intact in the mixture. Free amino acids appear early in the course of tryptic digestion, and they accumulate until about one-half of all the peptide linkages of the protein have been broken down. To split the remaining polypeptides requires the aid of the erepsin, which is present in the mucous membrane of the intestine. A similar enzyme is also present in other tissues of the body. Interesting investigations have been made on the exact degree to which trypsin-enterokinase can split the various known polypeptides. This seems to depend upon the structure of the polypeptide molecule and on the number of amino acids present in the chain. For example, alanylglycine, but not glycylalanine is hydrolyzed, although both contain the same amino acids but linked together in a different way; and tetraglycylglycine, which contains five glycine radicles, is hydrolyzed, whereas diglycylglycine, which contains only three, is not. It is important to remember that erepsin cannot act on proteins which have not previously been digested by trypsin. It seems to act only on polypeptides and indeed it may be a mixture of enzymes specific for each polypeptide. It is now known that the complete hydrolysis of proteins by crude trypsin is due to a group of enzymes, namely erepsin, aminopolypeptidase, carboxypolypeptidase, protaminase and probably others, so that the idea of trypsin as a single enzyme responsible for all of the proteolytic actions exhibited by the pancreatic juice is incorrect.

The importance of the presence of *erepsin* in the mucous membrane of the intestine would seem to depend on the fact that it serves as a barrier to the passage of any unsplit polypeptides from the intestinal contents into the blood. It helps to insure that the protein molecule be broken into its ultimate units before absorption. Since the discovery of erepsin and its rôle in further reducing protein materials to their constituent amino acids, the tendency has been to emphasize the individual amino acids as the final products always obtained. This may involve some error. From the study of allergic phenomena it appears unquestionable that at least traces of certain proteins may escape more or less the digestive agents and be absorbed in the form of molecules large enough to produce allergic responses.

Studies of the autolytic digestion which takes place in organs kept in a sterile condition after death indicate tryptic digestion to be different from other types in that it produces only small quantities of ammonia. The large quantities of ammonia produced in autolytic digestion no doubt have a relationship to the acids simultaneously set free during the process.

A very accurate technique for measuring tryptic activity is that based on the principle of the Gilman-Cowgill[46] method for estimating peptic power in which the emulsion on an exposed x-ray film is digested and the transmissibility

of the film to light before and after the digestion determined. When making measurements of tryptic activity, a different set of buffers is used to produce a pH in the alkaline range, in contrast to the pepsin tests where the digestions are carried out at an acid pH.

The Action of Lipase.—Neutral fat is decomposed into fatty acids and glycerol by the *lipase* present in pancreatic juice. This enzyme may also be extracted from the glands by means of 60 per cent alcohol or by glycerol, but it is insoluble in water. It acts in alkaline, neutral, or faintly acid media, and its action is remarkably accelerated by the presence of bile, and considerably depressed by inorganic salts. This favoring action of bile is undoubtedly owing to the bile salts (see page 975), and it is probable that this action is dependent upon the influence which these have in lowering surface tension and emulsifying the fat and therefore bringing about a more intimate contact between fat and water. The further functions of bile in favoring absorption will be discussed later.

The Action of Pancreatic Amylase.—The action of pancreatic juice on starch depends on an *amylase*. In animals having no active ptyalin in the saliva, pancreatic amylase serves as the only agent for handling this important carbohydrate. In any case, at least for the first stages of the disruption of the starch molecule—that is, its conversion into the dextrins—pancreatic amylase is a more powerful enzyme than ptyalin. It does not appear to be as efficient as ptyalin in the final stages of the hydrolysis, for it does not produce as much reducing sugar. Indeed extracts of pancreas will sometimes convert starch into soluble starch and dextrin with great speed, but produce scarcely any reducing sugar. On this account it is believed by many investigators that there are at least two distinct and separate enzymes in pancreatic amylase and also perhaps in ptyalin, one a true amylase which converts starch into dextrins, and the other a dextrinase which converts dextrins to maltose. In the case of both ptyalin and pancreatic amylase digestion proceeds best in a very weak acid reaction. Amylase, as it is secreted into the pancreatic juice, is fully activated; bile, apart from the alkali which it contains, has no influence on amylolytic power.

Besides amylase the pancreatic juice also contains *maltase,* and in the case of young animals or of those that take milk with their food throughout their lives, *lactase* also. After the suckling has discontinued taking milk, the lactase disappears from the pancreatic juice. Attempts have been made to bring it back by feeding the adult upon milk but without success. Occasionally the pancreatic juice also contains *sucrase* which splits sucrose to yield its constituent monosaccharides.

Digestion by the Intestinal Juice

The following enzymes have been found to be present in the secretion of the glands in the wall of the small intestine: erepsin, sucrase, maltase, lactase, enterokinase, and nucleases. All but the last-named have already been referred to. The nucleases consist of a group of enzymes which act on nucleic acid and various degradation products of it to yield a variety of substances. Different members of the nuclease group are also found in various tissues of the body, and presumably play a rôle in the production of the nucleotides and nucleosides known to be important in special processes, such as muscle contraction, for ex-

ample. The fact that nucleases are provided in the intestinal juice suggests that nucleic acid itself does not readily pass through the intestinal mucosa, and therefore some disintegration of its molecule is necessary.

The Action of Bile

One of the main functions of the bile salts is in assisting not only in the digestion but also the absorption of fats. When bile is excluded from the intestine, the feces are found to contain large amounts of fatty acids which have been split off partly by the now less effective lipase and partly by the action of bacteria. The fatty acid thus liberated in the absence of bile salts is not absorbed, because the bile salts serve as the carriers of fatty acids into the epithelial cells and the lacteals. This they do by their hydrotropic action. The influence of bile salts in assisting the action of pancreatic lipase is probably due to a lowering of the surface tension, thus promoting a more intimate contact of water with fat. This accelerating influence has also been demonstrated with synthetic bile salts, showing clearly that it is really these and not any other constituents of the bile that are responsible for its accelerating influence.

Bile also plays a very important rôle as a *regulator of intestinal* putrefaction. In its absence the stools become extremely putrefactive and the individual suffers from severe constipation. Bile itself is a favorable culture medium for certain bacteria, and therefore its value in counteracting these conditions cannot be due to any antiseptic action. In all probability the favorable action of bile is due to its moderate laxative action, by which the intestinal contents are expelled before the bacteria have grown to any great extent in them. The favorable action of bile on the action of trypsin and pancreatic amylase appears to be due very largely to the alkali which it contains.

The bile also serves as a channel of excretion. It is the only body fluid which dissolves cholesterol to any appreciable extent, and this property is probably due to the presence of the bile salts. Many toxins, metallic poisons and metabolites have been shown to leave the body by way of the bile.

The Chemistry of Bile

Bile contains a variety of substances, both organic and inorganic in nature. It is not our purpose to discuss the chemistry of bile in great detail. It is pertinent to point out some of the peculiar features of bile composition. The most characteristic substances found in bile are the bile salts, cholesterol, and the bile pigments.

The Bile Salts.—In most animals the bile salts consist of the sodium salts of glycocholic and taurocholic acids. Each of these acids is composed of a part called cholic or cholalic acid which is more or less related in chemical structure to cholesterol, and of glycine ($CH_2NH_2.COOH$, amino-acetic acid), or taurine ($C_2H_7NSO_3$, amino-ethyl-sulfonic acid), a derivative of cysteine, which is α-amino-β-thiopropionic acid ($CH_2HS.CHNH_2.COOH$). The cholalic acids form a series, the exact acid in different biles not being necessarily the same; for example, that in the bile of the pig is different from that in man. Bile salts are produced only by the metabolism of the liver cells. This fact has been demonstrated in remarkable fashion by experiments on dogs, the livers of which have been removed by the ingenious operative technique of Mann and his

associates.[82] It is the cholic acid part of these compounds that is manufactured exclusively by the liver cells; taurine and glycine can be synthesized by other tissues.

The source of the taurine has been studied, because this substance contains sulfur and the sulfur-containing compounds present in protein, namely, cystine and methionine, appear to be essential constituents of the diet. It seems that taurine cannot replace cystine and methionine in the diet and that the body's store of taurine is limited; the formation of taurocholic acid is diminished if cholic acid is given for a considerable period without a concomitant administration of cystine; on the other hand, the supply of glycine appears to be inexhaustible, as this substance may be synthesized in the kidney from urea.

There is considerable variability in the relative amounts of taurocholic and glycocholic acids in the bile of different animals. Human bile contains a relatively small amount of taurocholic acid; on the other hand, the bile of the dog contains a large excess of it.

Cholesterol.—This is one of the sterols (solid alcohols). These substances are usually complex monohydric alcohols and are widely distributed in the tissues and fluids of both animals and plants (phytosterols). Cholesterol itself is an unsaturated secondary alcohol and is closely related to the coprosterol of the feces which, however, is saturated. It exists in the body partly in a free state and partly combined with fatty acids to form esters. There is considerable evidence that the concentrations in the blood of free cholesterol and the esters are influenced by changes in the intermediary metabolism of fat as well as in the transport of this foodstuff in the body. Cholesterol is highly insoluble in water; bile is the only body fluid which dissolves it to any appreciable degree. So far as we know, this cholesterol in bile is in the process of being excreted and represents that formerly present in broken-down erythrocytes and other cells; it is possible that some of it is exogenous being derived from the food. The cholesterol in bile is particularly important because it contributes to the formation of gallstones, from which, in fact, the word cholesterol (solid bile) is derived; it may constitute from 20 to 90 per cent of the gallstone, the remainder being organic matter, such as epithelial cells, inorganic salts, pigment, etc. Evidently the animal body can synthesize cholesterol. This is indicated by the fact that the sterols in the feces of herbivorous animals are not the phytosterols of the plants which they eat but are derivatives of cholesterol; furthermore, hens continue to lay eggs containing cholesterol when fed on diets devoid of it.

The bile salts are hemolytic whereas cholesterol is antihemolytic. It is not inconceivable that this is related in some way to the fragility of the red blood cell and thus to the anemia problem. Another very important biological property of cholesterol and its related compound ergosterol, which was originally found in ergot, concerns its relationship to vitamin D (see page 828). Evidently there are several derivatives of these two sterols which have vitamin D properties.

The Bile Pigments.—The pigments of the bile are *bilirubin* and *biliverdin*. The latter is produced from the former by oxidation. If the oxidation is carried a stage further, a blue pigment called bilicyanin is formed. This process of oxidation can be observed in the ring test for bile pigment with fuming nitric acid. When bilirubin is reduced, urobilin, one of the pigments of the urine,

is formed. Bilirubin must therefore be considered as the mother substance of all these pigments, and it is of interest in connection with its derivation to know that it has the same empirical formula as iron-free hematin or hematoporphyrin, which is produced by treating hemoglobin with concentrated sulfuric acid. Experiments have shown that in albino animals the injection of hematoporphyrin seems to sensitize the organism to light. This suggests that in the formation of bilirubin from the hemoglobin of red blood cells the body produces hematoporphyrin which is toxic, and this is altered in some way to yield an isomeric compound which is nontoxic.

Chemical investigation has shown that bilirubin is built up from substituted pyrrols, of which four are probably contained in the molecule. The pyrrol group is also present in indole and tryptophane; it consists of four carbon atoms and an NH group linked together as a ring. Similar pyrrol derivatives can be produced by decomposing chlorophyll, the green coloring matter of plants. It is important to remember that bilirubin is acid in nature, and therefore can combine with alkalies to form salts. The relative amounts of bilirubin and biliverdin vary in the bile of different animals.

When these pigments enter the intestines, they are reduced to urobilin, part of which passes out with the feces, another part being absorbed into the blood and excreted in the urine. Part of that excreted in the urine exists, however, as a chromogen called *urobilinogen*. The urobilinogen is converted into urobilin by the action of oxygen.

CHAPTER LXVII

BACTERIAL DIGESTION IN THE INTESTINE

On an average diet, in twenty-four hours, the feces of man weigh about 100 grams, or after drying, about 20 grams. About one-fourth of the dry matter may consist of the bodies of bacteria. If plated out by the ordinary bacteriologic methods, however, it will be found that only a small proportion of these bacteria are living. The greater number have been destroyed, probably by the action of mucin in the large intestine. The nitrogen content of the feces amounts to about 1.5 grams a day, of which about one-half may be bacterial nitrogen. If the diet contains large quantities of cellulose material, as in green vegetable food and fruit, the mass of feces as well as the bacterial content may be considerably greater.

The foregoing facts indicate that very extensive bacteriologic processes must be going on all the time in the intestinal contents, and the question arises as to whether such action is beneficial or harmful to the animal economy. To answer this question interesting observations have been made on the growth and well-being of animals excised from the uterus under strictly sterile conditions and maintained thereafter on sterile food. Such observations made on guinea pigs have shown that the animals thrive and grow for a considerable time. Experiments carried out on chicks have not, however, yielded similar results. Chicks hatched out from the egg under strictly sterile conditions and then fed on sterile grain, do not thrive, but do so if the grain is mixed with a certain amount of fowl excrement. These two sets of experiments, apparently contradictory in their results, show that for certain groups of animals bacteria are required, but not for others.

It will be remembered that the size of the large intestine varies considerably according to the nature of the diet (see page 947). Animals taking great quantities of cellulose foodstuffs have very large ceca and very long intestines, whereas those which, like the cat, live practically entirely on cellulose-free food, have a rudimentary large intestine. The size of the lower intestine is obviously correlated with the presence or absence of cellulose in the food. It will be remembered also that the forward movement of the contents of the large intestine is very slow; indeed special provision is made, by the presence of the so-called antiperistaltic wave, to delay its movement. This suggests that an important digestive process must be proceeding in this part of the gut. In these ways conditions become established in the cecum for the active operation of bacteria. They attack the cellulose, and liberate the more digestible foodstuffs contained in the vegetable cells, also producing from the cellulose itself materials of nutritive value. The acids that are also produced by this process are neutralized by the carbonates secreted by the mucosa. In the ruminants bacterial digestion in the cecum is not relatively of such importance, because it takes place mainly in the paunch. The food mixes in this part of the stomach with the saliva, so that bacteria and ferments called cytases, contained in it, attack the cellulose, liberating the more easily digested foodstuffs enclosed within the cell walls. As this process goes on acids accumulate in the digestive mixture. The food is then returned to the mouth and chewed over again, after which it is swallowed into the main stomach, where it is digested.

The aid which bacteria render digestion depends therefore on the nature of the diet. Man, being omnivorous, stands midway between the two groups of animals discussed above. Although the cellulose contained in his food is not itself sufficiently digested to furnish nu-

triment, yet it is so far acted upon as to permit the rupture of the cell, the contents of which are then digested. The cellulose is, however, of value in furnishing bulk to the intestinal contents—"intestinal ballast" it is sometimes called.

In the small intestine of man there are bacteria capable of acting on carbohydrates and producing from them organic acids, such as lactic, acetic, etc. So long as a sufficiency of carbohydrate exists to encourage the action of these bacteria, others having an action on protein do not seem to thrive. It may be that this is to be accounted for partly by the production of acid substances by the carbohydrate fermentation, and partly by the fact that, as soon as the protein molecule is broken down by the digestive enzymes, its amino acids are absorbed. It appears, also, that the nature of the carbohydrate being acted upon plays some rôle. The acid-producing organisms—*B. acidophilus,* for example—thrive much better when lactose is present in appreciable amounts in the food; this is a specific effect, for other disaccharides do not favor the growth of the aciduric forms. If the stools contain a great abundance of *B. acidophilus,* 90 per cent, for example, they are not putrefactive, and therefore do not yield an offensive odor; furthermore, the production of intestinal gas is greatly reduced. There are probably also bacteria in the small intestine capable of splitting fat into fatty acid and glycerol, but practically nothing is known of their action. In the large intestine of man, there are also protein-digesting bacteria. These organisms belong to the class, of which *B. coli communis* is an example, the various members of which are known as facultative anaerobes because they can grow in the presence or absence of oxygen.

If bacterial growth is excessive or there is an insufficiency of carbohydrates in the small intestine, the bacteria attack the amino acids produced by the digestive enzymes and decompose them into products that may be toxic if absorbed into the blood.

BACTERIAL DIGESTION OF PROTEIN

From the standpoint of pathology, the most important action of bacteria is that which takes place on protein. Under anaerobic conditions the intestinal bacteria have in general the power of splitting off the amino group, deamination, whereas under aerobic conditions they split off the carboxyl group. The latter process may take place either before or after the removal of the amino group.

If oxidation happens *after* deamination, the products are not highly toxic and include phenol, cresol, indole and skatole, which are partly absorbed into the blood and partly excreted with the feces.

The fractions of those substances that are absorbed into the blood have their toxicity removed by conjugation mainly with sulfuric acid to form the so-called *ethereal sulfates.* A part is also combined with glycuronic acid. In the case of phenol and cresol this conjugation occurs immediately after absorption, but in the case of indole and skatole it is preceded by an oxidative process, converting these substances into indoxyl and skatoxyl, respectively. This detoxication process occurs in the liver, as has been shown by experiments in which this organ was artificially perfused outside the body. The sulfates are removed from the blood by the kidneys and excreted in the urine. The proportion of ethereal sulfates in this fluid therefore gives an estimate of the extent of intestinal putrefaction of protein. The indican, being readily detectable by the well-known

color reaction of Jaffé, serves as an indicator of excessive intestinal putrefaction. The indole and skatole which are not absorbed and detoxicated are excreted in the feces to which they give the characteristic odor. The source of the phenol is tyrosine and that of indole is tryptophan. The reader is referred to textbooks of biochemistry for information concerning the chemical process involved in the formation of phenol, indole and skatole.

If oxidation occurs *before* deamination, highly toxic substances called amines are produced. They are the so-called *ptomaines*. From alanine, ethylamine is formed; from tyrosine, hydroxyphenylethylamine; from histidine, iminazolylethylamine, and so on. The process of formation is illustrated in the accompanying formulas:

1. $CH_3 \cdot CH(NH_2) \cdot COOH = CO_2 + CH_3 \cdot CH_2(NH_2)$
   (alanine) (ethylamine)

2. $C_6H_4(OH) \cdot CH_2 \cdot CH(NH_2) \cdot COOH = CO_2 + C_6H_4(OH) \cdot CH_2 \cdot CH_2 \cdot NH_2$
   (tyrosine) (hydroxyphenylethylamine or tyramine)

3. $C_6N_2H_3 \cdot CH_2 \cdot CH(NH_2) \cdot COOH = CO_2 + C_5H_3N_2 \cdot CH_2 \cdot CH_2 \cdot NH_2$
   (histidine) (iminazolylethylamine or histamine)

Similar substances are very common among the metabolic products of plants; for example, they are present in infusions of ergot. They are also no doubt produced in the tissues of mammals, histamine being thus produced, as well as adrenaline which is the hormone of the medulla of the adrenal gland, and may be described as a methylated ethylamine derivative of tyrosine. It is therefore related to tyramine.

Physiological Effects of Bacterial Decomposition Products.—The great importance attached to these decomposition products of proteins depends on the fact that they have powerful pharmacological actions. Most of the amines when injected intravenously cause the arterial blood pressure to rise owing to constriction of the arterioles. This effect becomes more pronounced as the amine increases in molecular weight; for instance, ethylamine has a feeble effect, with tyramine it is marked, and with epinephrine it becomes maximal. This action simulates that of the sympathetic nerves so that it is called sympathomimetic. Not all amines develop this type of action. Some may bring about a lowering of the blood pressure; histamine, for example, causes the capillaries to become dilated. In larger doses, serious nervous symptoms and a condition of profound collapse are produced by amines. This has led several investigators to believe that the persistent occurrence of bacterial fermentation and the absorption of the resulting decomposition products of protein into the blood ultimately cause arteriosclerosis and the other symptoms that accompany senescence. It is difficult at the present time to evaluate such claims and beliefs.

If the ptomaines have formed in the food before it is eaten, the symptoms develop in from one to five hours after the meal, but if the decomposition occurs in the intestine on account of bacteria that are taken at the same time as the food, the ptomaines may not have developed sufficiently to cause symptoms until after twelve to forty-eight hours; sometimes, however, they develop in an hour or so. Prominent among the symptoms is usually diarrhea, which may be regarded as a protective reaction intended to remove the offending bacteria and ptomaines.

Actual infection of food with bacteria of the paratyphoid-enteritidis type is much more common than poisoning by substances (ptomaines) that have been generated in food before it is taken (Jordan). Meat, milk and other protein foods are usually the carriers of the bacilli, and in most of the accurately recorded cases the meat or milk was found to be derived from animals suffering from enteritis or some other infection. Sometimes, however, perfectly good food may become infected by handling.

The term *autointoxication* has been used frequently to describe the condition believed to be due to excessive intestinal putrefaction with absorption of the various products. It is not intended that this volume shall deal extensively with clinical medicine, and therefore extended discussion of autointoxication will be avoided here. We might point out, however, that the term toxemia is too often used to signify a condition that fails to fall clearly into any other category; the symptoms are not sharply defined but vague and indefinite. The earlier view, put forward by Metchnikov, that buttermilk is valuable because it supplies acid-producing bacteria to counteract the activity of the putrefying types, has had extensive reinvestigation by Rettger and associates.[107] These investigators have shown that the organism *Bacillus acidophilus,* a normal inhabitant of the intestine of the healthy breast-fed infant, can be implanted in the intestine of the adult by feeding the live culture along with one of the carbohydrates lactose or dextrin; in favorable cases the implanted organisms may be present to the extent of 90 or more per cent of the viable bacteria found in the stool. Foods play a rôle in this process, lactose and dextrin proving to be particularly valuable. Inasmuch as lactose is the carbohydrate found in milk, this food proves to be an excellent vehicle for the bacteria, hence the use of so-called acidophilus milk in the treatment of autointoxication, constipation, etc. The fact that lactose and dextrin are the only carbohydrates found to favor the implantation of *B. acidophilus* shows that the action is not due merely to the production of acid in the fermentation; many other sugars readily yield acid yet do not favor in peculiar fashion the growth of these organisms. Therefore the older view, that ingestion of a high carbohydrate diet should suffice to bring about favorable change in the intestinal flora, is inadequate. Acidophilus milk therapy has been found to be effective in many cases of diarrhea as well as of constipation; it may also be used to advantage in treating milk allergy.

The exact cause of the *toxemia that develops during high intestinal obstruction* has been a subject of debate. Whipple and associates[123, 124] have contended that a "perverted secretion" is formed, that a toxic proteose is produced and absorbed, and that animals can be immunized against this proteose. Such an immunological reaction has been denied by C. Dragstedt and Moorhead.[31] Another explanation is that offered by L. Dragstedt et al.,[34] who found that rapid distention of closed intestinal loops by secretion occurs in many cases to the point of perforation and peritonitis. When provision for the onward passage of the pancreatic juice and bile was made, Jenkins[66] found that closed loops of the upper intestine did not lead to such early death of the experimental animals. There is no doubt that the intravenous injection of commercial peptone results in a picture of toxemia, characterized by great increase in urinary nitrogen, sulfur and phosphorus, fall in blood pressure, failure of the blood to clot, etc.; but whether this picture is the same as that observed in animals with high intestinal obstruction is a question. The recent work of Dragstedt and Ellis[33, 35] indicates that failure of prompt resorption of the secretions of the stomach and pancreas produces equally profound disturbances.

The reaction of the intestinal contents has been studied by many investigators and found to undergo some variations. Long and Fenger[76] found that in man the contents of the duodenum vary from slightly acid to distinctly acid, depending upon the location of the end of the tube with reference to the pylorus; lower down in the duodenum the action was as frequently acid as alkaline, the degree of acidity, however, being so slight as to favor rather than hinder the digestive powers of the pancreatic juice. Using the intestines of slaughtered animals, it was found that the contents of the last third of the small intestine were often alkaline but might be more acid even than those of the first third, which were usually faintly acid in reaction. There were considerable variations, however. It has been found that the administration of lactose, which favors the growth of aciduric organisms, results in a more acid reaction in the lower intestine; in chicks, the use of lactose can bring about a definitely acid reaction in the ceca which is particularly valuable in preventing the growth of the pathogenic coccidia in this species. From these and other indications in the literature, it appears evident that the intestinal contents can show some variation in reaction, and the

character of the food eaten plays some rôle in producing this change. Some of these changes have been believed to be important in relation to the most effective utilization of ingested calcium, phosphorus, iron, etc.

We should not leave our subject without some reference to *the presence of vitamin B in the intestinal excreta.* If a rat is housed in a false-bottom cage which allows the feces to fall through, it is found that twice as much vitamin B_1 must be fed in the diet to meet the requirement of the organism. Coprophagy on the part of the rat is thus a protective reaction. There is evidence that the great growth of bacteria in the rumen of the stomach of ruminants is associated with the production of vitamin B which in turn is utilized by the host; by this arrangement, these animals are protected against the development of a deficiency with respect to this vitamin. Tests have also revealed that the vitamin B_1 in the stools does not represent an excretion of vitamin through the intestinal wall. In all probability the vitamin present in the intestinal excreta is that contained in the dead bodies of the bacteria, and is not the result of production of the vitamin and its discharge by a secretory process into the medium surrounding the bacterial cell. It has been found that the presence of fat, as well as particular carbohydrates, in the ingested food plays some rôle in this process, probably by affecting the growth of the bacteria themselves; also, that other members of the vitamin B complex are similarly affected.

CHAPTER LXVIII

ABSORPTION FROM THE ALIMENTARY TRACT

In a general way it may be stated that the function of digestion is to break the relatively complex molecules of which the organic foodstuffs are constituted into simpler ones which are capable of absorption. Proteins are broken down to amino acids or very simple combinations of them; fats are split to yield glycerol and fatty acids; the complex polysaccharides are decomposed to give a mixture of their constituent monosaccharides. This simplification might lead one to expect that the mechanism by which absorption occurs is one merely of physical diffusion, but it is much more than this, since an element of selective action also comes into play. This is evident even for inorganic salts and the simple sugars. For example, sodium sulfate is absorbed from a loop of intestine much more readily than sodium chloride, and blood serum is completely absorbed although, obviously, the osmotic pressure due to its solutes is the same as that of the blood.

ABSORPTION FROM THE STOMACH

From the experimental work done on this question, it appears that the stomach cannot be regarded as an absorptive organ. This problem has been studied in at least two ways. The pylorus may be occluded in anesthetized animals, the test substance introduced into the stomach and then the gastric contents examined after a period. Meltzer used this technique in demonstrating that strychnine, for example, is not absorbed in the stomach; only after the ligature around the pylorus was removed and the gastric contents allowed to pass into the intestine could the symptoms of strychnine poisoning occur. Another method, which is doubtless more physiological, consists in preparing a duodenal fistula in an experimental animal, a dog, for example, then feeding the test substance, and collecting for analysis all of the material discharged through the fistula. London has made many observations based on use of this technique. The facts concerning absorption in the stomach will now be summarized.

Water.—When given alone, water is practically unabsorbed in the stomach. It quickly passes through this organ into the intestine. We have already commented on the fact that liquids pass through the stomach much more readily than solid materials, and this fact is difficult to harmonize with the Cannon theory of acid control of the pylorus. It is well to bear in mind in this connection, however, that not all liquids escape absorption from the lumen of the stomach. Alcohol is absorbed to a considerable extent. Water mixed with alcohol in varying proportions appears to undergo some absorption along with the alcohol. This fact is of clinical interest. Many attempts have been made to secure absorption in the stomach of therapeutic agents that are sensitive to digestive enzymes, particularly those in the intestine, and in a large proportion of these experiments alcohol has been used as the important absorptive constituent of the solutions tried. Oral administration of insulin has been attempted by such means.

Carbohydrates.—It appears that for any of the common sugars to be absorbed from the stomach the solutions must be fairly concentrated (5 per cent or more). When one considers this fact together with the observation that of the common foodstuffs carbohydrates leave the stomach the earliest, it must be concluded that such an absorption of sugars is of little practical significance.

Proteoses and Peptones.—These substances are the result of peptic digestion of native proteins in the stomach. Therefore the question of their absorption is an important one and it has been investigated experimentally. From the work of London, who used dogs with a duodenal fistula, it appears that there is practically no absorption of protein or its digestive products in the stomach.

Fats.—Of the three common foodstuffs fat has been shown to remain longest in the stomach. This suggests that fat may be absorbed to an appreciable extent. If fat is held in the stomach for many hours, its escape being prevented by ligation of the pylorus, histological evidence of fat absorption through the gastric mucosa can be obtained (Inouye). The conditions of such experiments are so unphysiological, however, that this amount of absorption can hardly be regarded as significant. Under ordinary conditions, there is practically no absorption of fat from the stomach.

Salts.—Salts are only slightly if at all absorbed from the stomach. The concentration of the salt has been shown to be a factor. For example, Brandl has claimed that when the concentration of sodium iodide is 3 per cent or greater, appreciable absorption may occur. The presence of alcohol seems to facilitate this absorption. Under more physiological conditions, however, it appears that sodium iodide, and many other salts as well, is practically unabsorbed. This behavior of sodium iodide has been made the basis of a simple gastric motor function test.

Summary.—From the experimental work done on this question, it appears that the stomach cannot be regarded as an absorptive organ. Any absorption that has been shown to occur is so slight as to be of little physiologic significance.

ABSORPTION FROM THE SMALL INTESTINE

The methods described above in the discussion of absorption from the stomach have also been used to study absorption from the small intestine. Examination of the material discharged through a fistula at the ileocecal valve indicates that the absorption of the products of digestion through the wall of the small intestine is remarkably complete. Fatty acids and glycerol, the results of fat digestion, undergo synthesis into neutral fat during the absorptive process, the resultant fat being taken up largely by the lymph vessels. Carbohydrates pass into the blood as simple sugars, monosaccharides. Proteins are absorbed into the blood as amino acids or relatively simple combinations of them, the peptides. Water is readily absorbed. Inasmuch as the chyme passing through the ileocecal valve is always fluid or semifluid in nature, any absorption of water that takes place during the absorption of a meal may be compensated for, in part at least, by secretion of it in order to maintain the liquid character of the chyme. When water is taken to alleviate thirst, much of it is undoubtedly absorbed in the small intestine. Sodium chloride readily passes through the intestinal wall into the blood stream, and this passage does not

seem to be entirely a matter of simple diffusion due to difference in osmotic pressure or other purely physical causes. In view of the fact that studies have indicated some differences to exist in the mechanisms of absorption of water-soluble substances as compared with the products of the digestion of fat, it is pertinent to discuss these two mechanisms in some detail.

Absorption of Water-Soluble Substances.—It has already been pointed out that the intestine exhibits a remarkable selectivity with respect to the absorption of many materials. Perhaps the most striking example of this is found in the case of the simple sugars. This has been investigated by C. F. Cori and G. T. Cori,[26] who devised a method for studying the rate of absorption, which is far superior to that previously employed. In Cori's method, the entire gastrointestinal tract of small animals, such as the rat, is employed. The animals, kept for some time previously on a standard diet, are starved, either for twenty-four or forty-eight hours, after which 2 or 3 ml. of a strong solution of sugar are placed in the stomach, through a small flexible catheter which can be passed by way of the mouth. The rate of absorption is ascertained by subtracting from the amount of sugar that was given, the amount found by analysis of the gastrointestinal contents on killing the animals after varying intervals of time. Cori and Cori state that when sufficient sugar is given, the amount absorbed is constant from hour to hour, at least up to four hours, and they define as the *coefficient of absorption* that number of grams of sugar absorbed per 100 Gm. of body weight per hour. This is characteristic for each sugar, but it varies according to the time the animal was starved prior to giving the sugar. It is independent of the initial concentration of the sugar solution in the intestine.

For the monosaccharides the coefficients, determined after a starvation period of forty-eight hours, are as follows: *d*-galactose, 0.196 Gm.; *d*-glucose, 0.178 Gm.; *d*-fructose, 0.077 Gm.; *d*-mannose, 0.034 Gm.; *l*-xylose, 0.028 Gm.; and *l*-arabinose, 0.016 Gm. A high degree of selectivity, independent of molecular weight and definitely related to molecular structure, is thus revealed. The pentoses are absorbed at a rate which is about one-eighth that of the better known hexoses. It is evident that the slight stereoisomeric difference between glucose and mannose makes a sharp difference in their coefficients of absorption. The only possible source of inaccuracy in the Coris' method is destruction of the sugar by intestinal bacteria, but it is stated that this does not occur. These results are in sharp contrast with those obtained in a study of absorption from the peritoneal cavity. In this case C. F. Cori and Goltz found that the different sugars are absorbed at equal rates which diminish with time. Obviously the concentration affects the process. By analysis of the so-called free sugar of the tissues it was found that when different sugars are injected intravenously they pass very rapidly and at equal rates from the blood into the liver and muscles. It requires a shorter time for equilibrium to be attained between blood and liver than between blood and muscle; this difference is probably dependent upon differences in blood supply.

The rate of absorption of fructose from the gastrointestinal tract is less than half that of glucose. Consequently, the ingestion of a given amount of fructose might be expected to have less effect on the level of blood sugar than the taking of a corresponding quantity of glucose. Differences observed in blood sugar curves after ingestion of these sugars may be attributable, in part at least, to differences in speed of absorption and not wholly to a greater tendency for

fructose to be retained in the liver. This consideration casts some doubt on the validity of the fructose assimilation curve as a test of hepatic function.

The selective properties of the intestinal mucosa toward different sugars can also be demonstrated by the comparatively simple experiment of placing equimolecular solutions in isolated loops of intestine (of rabbit or cat) suspended in oxygenated Tyrode's solution at body temperature. The rate of diffusion can then be measured by determining the percentage of sugar in samples of the Tyrode solution pipetted off at intervals. So long as the loop remains alive, as evidenced by the presence of rhythmic contractions, it is found that glucose diffuses much more quickly than a pentose, such as xylose. As the strength of the glucose solution is increased, diffusion in a living piece of gut becomes progressively more rapid up to a certain maximal concentration which is about 3/4 mol (13.5 per cent) solution. It declines or remains steady at higher concentrations. In a dead piece of intestine the rate of diffusion is, of course, proportional to the concentration of the sugar solution. In a living gut pentose solutions diffuse out in proportion to their concentration.

It has already been stated that selective absorption by the intestinal mucosa applies to inorganic salts. In the case of these substances absorption may occur at one level and excretion at another. Thus calcium and iron are absorbed in the jejunum and upper reaches of the small intestine but excreted lower down; phosphate apparently is both absorbed and excreted readily at various levels of the gut.

Chemical change of a substance may occur during its absorption. This can be very readily demonstrated by the isolated living intestinal loop method described above. When a cane sugar solution is placed in such a loop, glucose and levulose diffuse out. If the loop be killed, cane sugar diffuses out. This effect cannot be due to the invertase of succus entericus but to the presence of the enzyme in the intestinal epithelium itself. Another instance of chemical change occurring during absorption is seen in the action of erepsin. This enzyme splits into amino acids the lower polypeptides which are the end products of the action of trypsin. Recent work by London and associates,[75] who used the angiostomy technique which permits the taking of samples of portal blood from the normal unanesthetized animal, shows that when a meal of protein is being absorbed, there is a considerable increase in polypeptides and related compounds in the portal blood. These findings suggest that proteins may not be absorbed simply as individual amino acids, as has been widely taught; either an appreciable fraction of the polypeptides are absorbed as such, or compounds of this sort are synthesized as the amino acids are passed through the cells of the intestinal mucosa. The latter possibility, if correct, would make protein absorption similar in part to that of fat.

The activity of the villi of the intestine has been studied. Wells and Johnson[121] have perfected a technique for observing the behavior of villi under various conditions. The mucosa of the intestine, as is well known, can function as both an absorbing and a secreting tissue. It appears that when it is in the normal resting state, the mucosa functions to absorb materials; when irritated locally by mechanical, chemical, or osmotic stimuli, hyperemia results, there is swelling of the villi, tonic contractions occur that are effective in impeding the venous and possibly the lymphatic drainage, and there is profuse secretion of fluid. Wells and Johnson suggest that secretion as well as absorption of

fluid is a physical process, and that transfer of fluid through the gut wall is regulated primarily by vascular reactions, both local and general. These studies have been extended by Nasset and Parry[96] to include determination of the rôle of pressure in the process. The absorption of glucose in aqueous solution was found to be independent of intraintestinal pressure between the limits of 5 and 25 cm. of solution below atmospheric. The secretion of sodium chloride and characteristic enzymes was found to increase in linear fashion with decreasing intraintestinal pressure. These results may help to explain some of the contradictory results reported previously; different workers may have had different pressure conditions operating in their experiments. There still remain unexplained, however, many features of the absorptive process.

Absorption of Fats.—As has already been pointed out, fat is digested by the lipases to yield glycerol and fatty acids. The fats are absorbed into the lacteal which lies in a central position in the villus, but the details of the mechanism by which they pass into the lacteal are not clear. The usually accepted teaching is that the fatty acids which are split off by the action of lipase are brought into a water-soluble state by the hydrotropic action of the bile salts (see page 975) and then enter the epithelial cells in solution where they recombine with glycerol to form neutral fat. The glycerol entering into this combination may have been absorbed as such, or it may have been produced by the animal itself, as is evidenced by the fact that neutral fat appears in the lymph of the thoracic duct after feeding a meal containing fatty acids, but no neutral fat and therefore no glycerol. It is possible that the body can make glycerol from glucose when the former is lacking in the diet. The synthetic process within the cells is possibly accelerated by lipase, at least it is easy to show that esterases, of which lipase is a type, can greatly accelerate the formation of an ester when added to a mixture of the alcohol and acid which form it. The reversible action of enzymes depends on the law of mass action. The difficulty of accounting for the synthetic action going on to any great extent in the presence of water may be resolved by supposing that the fat, as quickly as it is synthesized, is removed from solution, so that it can no longer have any influence on the reaction.

Whether this chemical theory of fat absorption be correct or not, there is one thing that is very evident as absorption proceeds, and that is the accumulation of fat in the epithelial cells. It occurs as fine particles which progressively become larger toward the base of the cells; the fat may even appear in the form of large globules. However packed with fat the cells may be, none is ever seen in the peculiar striped border which characterizes these cells. This fact is considered to show that the fat cannot have entered as such, but in solution. Another explanation, however, for the absence of fat from the free border of the cells is that this portion is composed of lipoid materials in which neutral fat is soluble, and that it is passed on to the underlying protoplasm where it is insoluble. That the free border is lipoid in nature is indicated by the fact that lipoid-soluble dyes, such as neutral red or toluidin blue, pass through it into the cells, whereas water-soluble dyes apparently pass between the cells, dissolved possibly in the water-soluble substance which cements the cells together.

There is evidence that the leucocytes can carry fat particles through the reticular tissue to the central lacteal of the villus. The exact details of this passage into the lacteal are not clear. Once inside the lacteal, the further

transference of the fat to the thoracic duct is readily accounted for. In this connection it is pertinent to remind the student, that studies of the thoracic duct lymph have shown that only about 60 per cent of the fat undergoing absorption is accounted for. This should doubtless be interpreted as meaning that this problem still calls for research. It has been suggested that contraction of the muscle fibers, running in the reticular tissue of each villus from the muscularis mucosae to the wall of the central lacteal, results in pumping of the lacteal fluid into the lymphatics of the mucosa. Such a mechanism is suggested by the anatomical arrangements, but recent observations[121] of the behavior of the villus during absorption of water-soluble materials do not support the "villus pump theory." Observations of direct absorption of fat by the villus apparently have not yet been made. Once the fat is within the lymphatics of the mucosa its onward flow is determined by valves, and it is probable that the segmenting movements of the intestine assist in maintaining the movement of the chyle, as the fat-laden lymph is called.

Attempts have been made to support the chemical theory of fat absorption by feeding a neutral fat possessing some characteristic that depends on the manner of union existing between fatty acid and glycerol, and then determining whether this fat appears in an unchanged condition in the thoracic duct. If it does, it must have been absorbed through the intestinal epithelium in an unbroken, unsaponified condition, for it is unlikely that in any resynthesis occurring in the intestinal epithelium the fatty-acid molecules would recombine with the glycerol molecules in exactly the same manner as before. There are, however, but very few qualities of neutral fats, apart from those of the fatty acids which compose them, by which they may be characterized. Optical activity has been suggested as a basis for the desired identification. Unfortunately, none of the ordinary fats is optically active, although from chemical considerations it is quite conceivable that some might be. Bloor prepared a synthetic isomannid-dilaurate which is readily absorbed and he found, on feeding it to dogs, that the chyle flowing from the thoracic duct did not contain any of it. This result confirms the previous work of Frank, who found that the ethyl esters of fatty acids are not absorbed unchanged. Had this occurred, as would be required by the physical theory of fat absorption, these fatty acids would have appeared in the chyle in optically active condition. A new possibility in this field is presented by the discovery of deuterium, the isotope of hydrogen, which can be detected when present in minute amounts. By synthesizing compounds containing deuterium and administering them to the living organism it has already been proved possible to show that the fat of the food, even when present in small amount, is largely deposited in the fatty tissues of the body before being utilized in metabolism.[128] The small supply of deuterium has made it necessary thus far to perform such experiments on mice. Artificial fats might be prepared containing deuterium, these fats administered by way of the alimentary tract, and the fatty chyle in the thoracic duct lymph examined for its content of the new isotope of hydrogen. Experiments of this sort might throw further light on the mechanism of fat absorption.

If resynthesis of neutral fat occurs during absorption, it is probable that its purpose is to permit a rearrangement of fatty-acid molecules to form a new fat which is more adaptable for use in the organism. The lecithins, which constitute the most important part of the fatty substances of the cell itself, are mixed glycerides, that is to say, compounds containing a variety of fatty acids. The rearrangement of the molecules of neutral fat which apparently occurs during absorption may be the first step in the transformation of fat into lecithin.

In order further to elucidate this question, Bloor has performed a number of interesting experiments in which the chemical properties of fats before and after absorption were compared. The criteria which he took were melting point, iodine number, and mean molecular weight. It was found that during absorption very considerable changes occur in these characteristics. The results therefore support the chemical rather than the physical theory of fat absorption.

Mineral oil is apparently absorbed from the intestine to some extent. Indeed Channon and Collinson[24] have actually succeeded in isolating 2 grams of liquid paraffin from the liver of a pig that had been fed this hydrocarbon, and

they showed that its absorption lowers the iodine value of the liver fat. Undoubtedly sterols, such as vitamin D, are readily absorbed. It seems highly improbable, if not wholly impossible, that chemical changes are indispensable for the absorption of such compounds. Logic, however, does not permit one to infer from this consideration that hydrolysis and resynthesis are not involved in the absorption of neutral fat. More pertinent to this question is the doubt cast by J. Mellanby on the belief that disruption of neutral fat is a necessary preliminary to its absorption; he has pointed out that there is no more lipase in the pancreatic juice of the cat than is required to produce enough fatty acid for the emulsification of the ingested fat. Some fat must therefore be absorbed directly and the hydrotropic influence of the bile salts is probably responsible for bringing this about. This view receives some support from the observations of Frazer[42-44] who devised a method for counting fat particles in the blood and reported differences in the blood particle counts in the systemic as contrasted with the portal circulation when olive oil, as compared with a mixture of fatty acids and glycerol, was fed to rats. Frazer interpreted his findings to mean that the portion of dietary fat which is hydrolyzed forms soluble complexes with bile salts and is absorbed into the portal circulation for storage or special metabolic transformation in the liver; the remainder of the dietary fat is absorbed without hydrolysis into the lymphatic system, and thus poured into the general circulation through the thoracic duct to be stored in the fat depots.

The absorption of fat is seriously impaired when the pancreas is removed. In depancreatized dogs kept alive with insulin for example, the feces are excessively fatty but become normal when pancreas is added to the daily diet. In man the absence of pancreatic juice is said to diminish the absorption of fat by 50 to 60 per cent. If the bile is also absent, the diminution amounts to 80 to 90 per cent, and in such cases the administration of bile or pancreas powder greatly improves fat absorption. Even when both bile and pancreatic juice are absent some of the fat is split and the feces contain fatty acid as well as fat. This is probably attributable to the action of small amounts of lipase present in the gastric and intestinal juices, but bile being absent, this fatty acid is not absorbed. From the work of Greaves and Schmidt[51] it appears that absence of bile interferes also with the absorption of fat-soluble vitamin A. These investigators studied the effects of various conditions, biliary fistulas, for example, on the requirement of the rat for vitamin A. Icteric rats had the same requirement as the normal animals, but failed to absorb as much when the dietary factor was administered by stomach tube. Essentially the same type of results with respect to the absorption of vitamin K has also been reported by Greaves.[50]

The observations of Flint[41] show that, provided they are fed properly, dogs tolerate quite well the surgical removal of as much as 60 per cent of the small intestines; curiously enough, they are unable to handle much fat. Evidently, then, the clinician cannot consider loss of pancreatic juice and bile as the only factors leading to interference in fat absorption; a certain amount of intestinal mucosa is important.

ABSORPTION IN THE LARGE INTESTINE

Knowledge of the extent to which absorption takes place in the large intestine is important because of its possible use in so-called rectal feeding. Water is readily absorbed from the lumen of the large intestine. We have seen that one

function of this part of the alimentary tract is to dehydrate the chyme, changing it gradually to the consistency of the feces. Sodium chloride is also absorbed. Inasmuch as bacterial action is most intense in this part of the gut, the products of bacterial action that get into the blood are doubtless absorbed largely from this region. There are certain important facts which bear on the rectal feeding problem. Fats and proteins are absorbed in such small amounts that it is useless for the clinician to attempt to administer these foodstuffs by way of the rectum. Glucose, however, is absorbed to a considerable degree when the concentration used is approximately 10 per cent. Coleman utilized these facts in developing his method for feeding patients with gastric ulcer.

Cowgill and Weinstein have recently studied the absorption of vitamin B placed in the large intestine of dogs provided with a valvular fistula of the large intestine. From their work it appears that the surgeon may administer this important dietary factor to a patient through a fistula of the large intestine, but that different sources of the vitamin show differences in effective absorption. For example, the artificial product formerly used as the international standard of vitamin B_1, a fuller's earth adsorbate, does not readily yield its adsorbed vitamin in the large intestine, in contrast to a solution of the vitamin which may also be given parenterally. Evidently, then, the clinician may administer vitamin B_1 to a patient with an artificial anus, but he should be careful to select a suitable source of the vitamin to use in such cases.

PART VII

THE ENDOCRINE GLANDS

By R. G. Hoskins

CHAPTER LXIX

HORMONES IN PHYSIOLOGY

The principle of the hormonal regulation of bodily functions was introduced into physiology relatively recently. It represents a special phase of chemical regulation comparable in principle to the chemotactic activities seen in the lowest forms of life, and as exemplified by the control of the respiratory center by acid metabolites. Unlike nervous regulation, that by hormones is necessarily generalized, because of the discharge of the active principles (*internal secretions*) directly into the blood stream and thence their distribution throughout the body. Such specificity of organ response as is manifested is secured by the special reactivity of the recipient organs.

The fundamental concept of hormone physiology appears in naive form in the early history of western medicine. Various diseases were believed to be due to lack of one or more mysterious substances supplied by the different organs. It followed that the resulting diseases were to be cured by supplying these lacking substances through ingestion of the organs themselves. This system of treatment came to be known as *opotherapy*. It was employed by Celsus and Dioscorides. Wolf's liver was used for hepatic disease, hare's brain for nervousness and the lung of the fox for respiratory disorders. As Paracelsus formulated the doctrine of opotherapy, "heart cures heart, spleen spleen, lungs lungs."

Modern interest in the internal secretions was aroused largely by the work of Brown-Séquard in 1889, though a considerable number of investigators had preceded him in the experimental field. Reviving the ancient doctrine of opotherapy this investigator was led to treat himself for general debility by injections of testicular extracts. His enthusiastic reports of beneficial results at once commanded worldwide attention.

The first to formulate the modern idea of endocrinology was Bordeu, a physician at the Court of Louis XV. Bordeu taught that each organ of the body is "the workshop of a specific substance which passes into the blood" and that upon these substances the physiological integration of the body as a whole depends. He described in some detail the secondary sexual changes that result from castration or ovariectomy. Berthold in 1849 was the first to make a formal experimental attack upon the problems of endocrinology. He restudied the effects of castration in fowl and discovered that the changes following that operation can be prevented by implantation of testicular tissue. Berthold inferred that the retention of the sexual characteristics was due to "the pro-

ductive relation of the testis, i.e., to its effect upon the blood and thence through the corresponding effect of such blood upon the entire organism.'' It was Starling who introduced the term *''hormone''* to designate the active principles of the endocrine glands. Its root meaning is ''excitor,'' but the term is in part a misnomer in that some of the hormones actually decrease functions. Sharpey-Schäfer[125] proposed to meet this difficulty by designating the internal secretions, as a group, by the term ''autacoids.'' Those which stimulate were to be called hormones and those which depress, *chalones*. The terms were somewhat widely adopted by British writers but have failed of general acceptance—largely, perhaps, because a single hormone, e.g.. adrenalin, can be either stimulating or inhibiting, depending upon the tissue affected.

The principal hormone-producing organs are the pituitary, the thyroid, the parathyroids, the adrenals, the pancreas, the stomach and intestines and the gonads. Recent work suggests that the pineal and the thymus glands may also produce true hormones. Until recently the endocrine organs were frequently designated as the *''ductless glands''* but the term is in part a misnomer since the pancreas, at least, has both ducts and endocrine functions.

Well before the advent of endocrine physiology, physicians were acquainted with several diseases now known to be due to glandular disorders. In 1786 Parry had come to recognize the chief features of *exophthalmic goiter*. Eight cases were collected by him and published after his death in 1825. In 1850 Curling observed that defective thyroid development is accompanied by certain of the manifestations now well recognized in the disease, *myxedema*. In 1840 Mohr reported a remarkable and fatal obesity in a woman who suffered from beginning imbecility, loss of memory, somnolence, and partial blindness. Postmortem examination showed degeneration of the pituitary body. The relation of the pituitary to gigantic stature was dimly apprehended by several physicians, beginning as early as 1784, and the specific relationship of this gland to *acromegaly* was clearly outlined by Marie in 1886. In 1849 Addison described the disease bearing his name and pointed out its dependence upon destructive changes in the adrenal glands.

The first actual demonstration of the physiological process of *internal secretion* was afforded by Claude Bernard who described the process in 1848. He discovered that the glycogen of the liver is discharged as dextrose directly into the blood stream. While the term, internal secretion, is no longer applied to indifferent substances like dextrose, Bernard's work is of outstanding importance to endocrinology, for it proved the possibility of the direct transference of chemical substances from organ to blood stream.

While no bodily function, apparently, is free of hormone control, those most notably so affected are the digestive functions, growth and reproduction. That hormone control represents a primitive mechanism is suggested by the fact that the internal secretions are interchangeable from one species to another. Thus insulin is quite as useful in the treatment of human diabetes whether it is obtained from the pancreas of man, ox or fish.

The hormones in some cases are fairly simple chemical substances; certain have been obtained as crystalline bodies, but others apparently are of protein nature and share in the complexity of the latter. Some are remarkably potent. Adrenalin from the adrenal glands can be shown to exert a definite effect in concentration as low as one part in four hundred millions. The

thyroid hormone is so potent that two milligrams suffices to increase the oxidative processes of an adult by one per cent. It is estimated that one gram suffices for a human being for five years.

The practical application of endocrinology in the treatment of disease lags far behind the available anatomical and physiological knowledge. The therapeutic use of thyroid, insulin, adrenalin and posterior pituitary extracts has often been conspicuously successful. On the other hand, the administration of parathyroid extract, extract of adrenal cortex and various hormones related to the reproductive functions has often been disappointing. Other preparations that have shown potency in laboratory experimentation have as yet had only limited use in human disorders. Endocrine research, however, must be judged not only by its immediate practical utility, but also by the light which it has thrown on disease processes in general. As Barr[14] says, "With increasing knowledge of the hormones, many common symptoms and maladies have acquired new interest. Ideas concerning pathogenesis have been transformed and previously unrecognized interrelationships have been revealed. Adiposity, hypertrichosis, abnormal pigmentation, hypertension, menstrual disorders, disturbances in carbohydrate metabolism, decalcification of the skeleton and polycythaemia are a few of the pathologic states in which endocrine influences can be demonstrated."

In their control of the bodily functions the hormones operate in three different ways. Some influence the tissues directly; for example, the mammary glands react to certain endocrine influences when all nerve connections are cut. A hormone from one gland may importantly determine the secretion of another; the most notable example of this is the influence of the anterior pituitary on the gonads, the thyroid and the adrenal cortex. Finally, hormones may act through their influence on the nervous system.

The control of hormone secretion has presented a difficult problem and one concerning which our knowledge is still seriously defective. In general, the endocrine glands seem to be capable of a considerable amount of autonomous activity, but their secretory level is likewise subject to a considerable amount of adaptive control. In addition to regulation by other hormones, as previously mentioned, nervous impulses have also been shown to be important in certain cases. The fact that a thyroid graft, for example, suffices to forestall symptoms of hypothyroidism suggests that one of the factors in holding the secretory rate at the optimal level might be something akin to the law of mass action, the level of output representing an equilibrium between "secretion tension" and quantity of hormone in the circulating medium.

A topic which has received little consideration and which is of fundamental importance in endocrine physiology concerns the factors determining the reactivity to a given hormone. Fragmentary evidence indicates that some of these factors are the pH of the reacting tissues, the temperature of the tissues or of the environment, the age and sex of the subject, the nutritional condition of the tissues and the available supply of vitamins. The electrolyte balance seems also to be of importance.

Some factors which probably influence both the tissue reactivity and the level of hormone production in the various glands are season, diet, environmental temperature, age, sex, the levels of activity of related glands and phases of the sex cycle. These aspects of endocrinology are all in need of further investigation.

The proof that any given bodily structure has an endocrine function presents a difficult problem. The conventional first step toward that proof is to extirpate the organ in question and note the changes produced. These could be due to the absence of a hormone or to a failure to remove from the blood stream one or another deleterious metabolic product. That is to say, the structure might function either by a process of addition or subtraction. Another classic approach is to administer gland substance or an extract of the organ. This method has the logical defect of not excluding chemical artifacts as the source of any reactions that may be observed. The precursors of the hormones may be highly labile and either postmortem changes or chemical manipulation may alter them into pharmacologically active substances that are significantly different from the true hormones. Strict logic requires that the hormone be identified in the blood as it emerges from the gland but with one or two notable exceptions this has not been technically practicable. The chief reliance of endocrinologists, therefore, has been a combination of the first two methods; namely, to demonstrate changes following removal of the given organ and restoration of the affected functions to normality by so-called "replacement therapy" with glandular derivatives. This combined method largely meets the logical necessities in fixing the status of any given derivative though it does not prove the exact identity of the derivative with the actual hormone in question. The possibility remains that the derivative may serve only as a precursor substance from which the body is able to derive the hormone. The method is chiefly defective as a means of determining the total hormonal activity of a given organ. In no instance do we yet know all of the results of any gland extirpation whereas logic requires that all perturbations be corrected by the replacement therapy. Certainly mere "survival tests" which are often relied upon are inadequate even though the experimental animal seems to maintain good health. Complete restoration of all functions to normal is the crux of the matter.

The literature of endocrinology has become extensive and is rapidly growing. A textbook discussion such as this can deal with but a relatively small proportion of the available facts. It should be regarded as only a means to orientation and should be supplemented by reading of the more exhaustive works. A few of these may be cited.[17, 39, 50, 57, 58, 69, 83, 125, 146]

An exhaustive bibliography of endocrinology is available in the *Index Catalog of the Surgeon General's Library,* supplemented by the *Quarterly Cumulative Index Medicus.* Several contributions in *Physiological Reviews* afford a considerable number of authoritative discussions of important endocrine topics. The same can be said of the successive volumes of *Annual Review of Biochemistry* and *Annual Review of Physiology.* The current literature is dealt with in the journals, *Endocrinology* and *Journal of Clinical Endocrinology,* which publish both original articles and abstracts. *Biological Abstracts* is another good source of information. Special monographs on the individual glands will be cited in subsequent sections of this discussion.

CHAPTER LXX

THE THYROID GLAND

The first significant experimental contribution to our knowledge of thyroid physiology was made by Schiff in 1858. He removed the thyroid glands from a series of animals and found that death soon ensued. But these observations made little impression on contemporary physiologists, who at that particular time "had little interest in biological researches or confidence in their results" (Meltzer); the fashion then was to try to explain all the phenomenon of life in direct terms of physics and chemistry.

It is to clinicians rather than to physiologists that we are indebted for our first practical enlightenment regarding thyroid functions. Gull, a surgeon, in 1873 reported the cases of five women whose puffy faces, bulky forms, scanty dry hair, and general lethargy were recognized as indicating a common disease process. Five years later Ord, who had made a study of such patients, secured an autopsy of one; from this it appeared that the thyroid gland was atrophic and that the general puffiness of the subcutaneous tissues was due to an accumulation of mucoid material. He therefore designated the new disease *myxedema*. At this time the introduction of antisepsis by Lister emboldened surgeons to begin to treat goiters by radical operation. In 1883 Kocher reported upon the after-effects of the complete removal of goitrous glands and emphasized the resulting interference with nutrition. Schiff was then led to extend his earlier experiments and learned that not only could various symptoms of myxedema be produced by extirpating the thyroid glands in dogs, but also that these symptoms could be ameliorated by thyroid grafts. Numerous other investigators soon confirmed Schiff's results in work on various animals.

Considerable confusion was caused in these earlier experiments by a lack of knowledge of the independent function of the parathyroids. Thus in carnivores, in which the thyroid and parathyroid glands are closely associated anatomically, tetany and other symptoms now known to be due to parathyroid deficiency were noted, whereas in herbivorous animals these latter effects were absent. It was not until Gley[51] recognized in 1891 the independent functional significance of the parathyroids that the paradox was explained.

Using the newly developed calorimeter, Magnus-Levy[95] in 1895 discovered that clinical hypothyroidism is characterized by a lowering of the heat production *(basal metabolic rate)*—in some cases as much as 40 per cent. A similar effect was soon found to be characteristic of thyroidectomy in animals. In most mammals, according to Marine,[96] the fall in heat production begins between the fifth and seventh days after the operation. It reaches its lowest level (minus 30 to minus 40 per cent) in from twenty days to two months. The depression persists throughout the remainder of the life of the subject except as it is mitigated by thyroid medication or by regeneration of thyroid remnants that may be left behind. The effects of the operation are more striking in young than in older animals. The lowering of metabolism in the young leads to deficient physical, mental and sexual development (vide infra). For the detection of

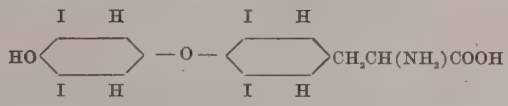
thyroid deficiency in clinical practice, determinations of the basal metabolic rate are of primary importance. In case of children in whom true "basal" rates are difficult to secure, the best index is the degree of skeletal development as brought out by skiagrams—especially of the wrists (Shelton[127]).

The thyroid is influenced by the nutritional state of the body. Excessive consumption of meat and, especially of liver, leads to overactivity; this, according to some authors, is followed by exhaustion of the gland and accumulation of colloid in its vesicles. Sea food, on the other hand, with its high iodine content, causes reduction in the size of the gland. Like proteins, fats also show a tendency to cause thyroid hypertrophy. Marine suggests that these reactions to food indicate that the thyroid hormone is more necessary to the oxidation of fats and proteins than of carbohydrates. Diets in which there is a serious imbalance of calcium and phosphorus together with iodine deficiency have been shown in dogs and rats to cause thyroid enlargement. On the other hand, general inanition causes involution of the thyroid with a decrease in the size of the epithelial cells and of the blood supply together with increase in the colloid and in the iodine store. These events are interpreted as indicative of decreased functional activity. Other evidence suggesting that the thyroid hormone plays a special role in the utilization of foodstuffs is that the "specific dynamic action" that normally results from their ingestion is materially lessened by thyroidectomy. The stimulating influence of food can be restored by thyroid feeding. Vitamin deficiency causes decrease in the size of the thyroid. This depression may be one of the mechanisms by which the nutritional manifestations of *avitaminosis* are brought about. The thyroid is susceptible to various other environmental influences. The gland is more active during the cold season and during periods of physiological stress such as puberty or pregnancy. Many cases of hyperthyroidism following emotional strain have been reported.

A special relationship between the thyroid gland and the element, iodine, has long been known. For more than a century the therapeutic value of iodine or iodine-containing substances in the treatment of goiter has been recognized. Several investigators in addition to Baumann[15] had made studies of the chemistry of thyroid substance but it was he who first (1895) was able to show that iodine in a firm organic combination is a normal constituent of this tissue. He treated the gland substance with 10 per cent sulfuric acid and obtained a brownish powder containing about 9 per cent of iodine which he named *iodothyrin*. He showed that the amount of iodine in the thyroid of dogs varies from one animal to another and that feeding iodine increases the amount. Four years later Oswald[107] observed that iodine is contained in the thyroid colloid and that the colloid is a globulin. He introduced the terms *thyroglobulin* and *iodothyroglobulin* which have since been much used in the literature. It was at first believed that these might represent true hormones of the gland. In man the thyroid gland contains as a maximum about twenty-five milligrams of iodine. In the calf this element has been shown to appear in the gland as early as the third fetal month. Seidell and Fenger[123] showed that there is a definite seasonal variation in the iodine content of the gland, it being relatively low in the spring and high in the late summer. The perfused living thyroid has been shown by Marine to have marked ability to select iodine from fluids circulated through it. The affinity of the thyroid for iodine can be shown also by feeding it to pregnant mothers and obtaining a

rapid storage in the fetal thyroids. Although iodine occurs in small amounts in various of the other endocrine glands, it is believed that the thyroid only has the ability of elaborating a hormone containing this element.

The next major step in the chemical investigation of the thyroid was reported by Kendall[77] in 1916. By means of alkaline hydrolysis he obtained a crystalline compound containing 65 per cent of iodine and showed that it produces various of the same pharmacologic effects as does thyroid substance itself. This compound he named *thyroxine,* a word coined from selected letters of the term "trihydro-tri-iodo-oxyindole propionic acid" which, he believed, represented the true hormone. In 1926 Harrington[59] improved the method of extraction and was able to secure better yields. He determined the empirical formula to be $C_{15}H_{11}O_4NI_4$. Structurally it is a tetra-iodo substituted derivative of the p-hydroxyphenyl ether of tyrosine or 3 ; 5 ; 3^1 ; 5^1 *tetra-iodothyronine,*



It appears that the mother substance from which natural thyroxine is elaborated is *l*-tyrosine. Marine believes that the true hormone of the thyroid is the iodothyroglobulin of Oswald and that thyroxine is only the active chemical group of this hormone. There are, however, some slight pharmacological differences between the two. In his earlier studies Kendall had obtained a physiologically inactive iodine compound which Harrington subsequently showed to be di-iodotyrosine. The latter has estimated that about 40 per cent of the iodine is in the form of thyroxine and 60 per cent in the form of di-iodotyrosine. These two substances appear to exist in a balanced state, the equilibrium point of which varies somewhat under different physiological or pathological conditions. Salter[120] has been able to synthesize an active agent, presumably thyroxine, by peptic catalysis of di-iodotyrosine.

The relationship of iodine to the thyroid gland is of special clinical importance in the condition known as *colloid goiter.* This condition is endemic in various districts throughout the world. It is a disorder in which the acini of the thyroid become distended with colloid, and the lining cells are flattened (Fig. 350). The gland may thus come to have a relatively enormous size, weighing a kilogram or more. Despite a great deal of study, the etiology of colloid goiter remains to some extent uncertain but most investigators assign predominant importance to deficiency of iodine in the food and drinking water. Of recent years increasing importance has been ascribed to a defective iodine-calcium balance in the food. The weight of available evidence supports the conception that the goiter represents an adaptive reaction, the low quality of the secretion being compensated in some degree by excessive production. From the standpoint of physiology the disorder is best regarded as a special case of hypothyroidism. The symptomatology varies from practically nothing to the full-blown picture of thyroid deficiency (vid. infra). The subject has been interestingly discussed by Marine.[97]

The clinical significance of the thyroid hormone centers largely in its relationship to metabolism. In 1893 Friederich Müller[101] discovered that in exophthalmic goiter (clinical "hyperthyroidism") the nitrogen metabolism as shown

by the nitrogenous metabolites in the urine is increased. The same effect can be produced in the normal animal by administering thyroid substance or thyroxine. Two years later Magnus-Levy[95] showed that in clinical hypothyroidism the rate of oxygen consumption (basal metabolism) is depressed—in marked cases as much as 40 per cent—and that the low rate can be raised to normal or above by feeding the gland substance. Proteins, fats and carbohydrates all share in the augmented oxidation. The means by which the thyroid hormone brings about the increased oxidation is not known, but the small quantity of the hormone that is required to produce a major effect suggests the action of a

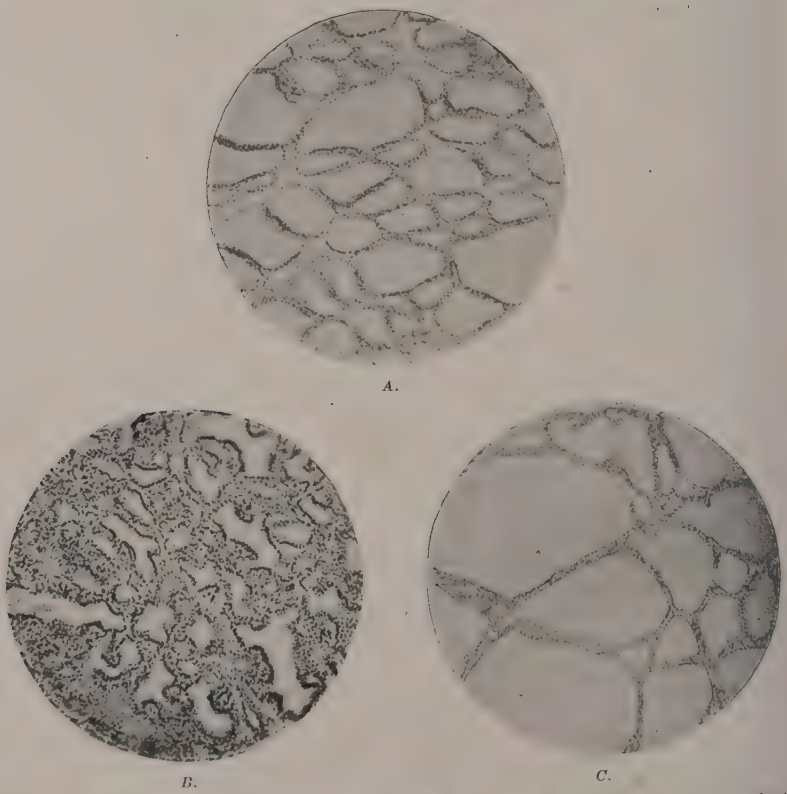


Fig. 350.—Microphotographs of thyroid gland of dog. *A*, normal gland; *B*, active hyperplasia; *C*, colloid goiter. (From Marine and Lenhart.)

catalytic agent. The influence of the hormone in the individual tissues persists for a considerable time as is shown by the increased oxygen consumption rate of surviving tissues taken from thyroidized animals. Conversely, as Ahlgren[4] has shown, muscles isolated from thyroidectomized animals consume much less oxygen than normal.

The thyroid hormone has an important influence on the processes of maturation and differentiation as contrasted with those of growth. The classic obser-

vation on this point is that of Gudernatsch[55] who reported in 1914 that the feeding of small amounts of thyroid substance to tadpoles results in their early metamorphosis to the adult form. Thus it is possible to produce a frog no larger than a house fly.

Another indicator that is sometimes utilized is the acetonitrile test of Reid Hunt[73] which depends upon the protection that thyroid hormone confers upon mice against this poison. It seems paradoxical that the same hormone decreases the resistance of rats, rabbits and guinea pigs to acetonitrile. The explanation has been offered that the reactions in both cases depend upon the increased metabolic rate of the recipient animals; in mice this leads to the production of an innocuous compound whereas in the other species the end-product is toxic.

Various other methods of assay are described by Munch.[102] Of recent years determinations of the iodine titer of the blood has been used clinically to some extent as an index of thyroid activity.[91]

It seems probable that physiological processes in general are stimulated by the thyroid hormone. This is indicated not only by the increased rate of oxygen consumption but also by the wasting of tissues and an increased reactivity of the nervous system. The stimulating influence is manifested in such symptoms of clinical hyperthyroidism as rapid pulse, insomnia and nervousness. The fact that the irritability of the sympathetic nervous system is increased is utilized in the "Goetsch test" for hyperthyroidism; a "positive" reaction amounts especially to an increased cardiovascular response to a standard injection of adrenalin.

Much of the physiology of the thyroid is exemplified in the symptoms of *thyroid deficiency* (hypothyroidism) in experimental animals or in man. When the deprivation is set up in infancy the most evident result is retardation in growth and development. When the gland is atrophied at birth the condition known as *cretinism** soon develops (Fig. 351). Ossification of the skeleton is retarded, hence bowing of the legs is common. Even though the cretin lives into adult years normal size is not attained. Brain development is sluggish with resulting deficiency of intelligence. The eyes are dull and lusterless and the face shows lack of animation. The human infant is slow in beginning to walk. The sex organs remain small and commonly fail to attain functional activity. The tonus of the muscles is low, a fact that accounts for the protruding abdomen that is characteristic of thyroid deficiency. This hypotonicity is shared by the smooth muscles, hence chronic constipation is common. The temperature of the body is somewhat subnormal and this is accompanied by a subjective sensation of chilliness. The skin is thickened and rather poorly nourished and the hair is coarse, sparse and dry. The teeth are slow in appearing and have little vitality; even with good dental care they are frequently lost. Commonly, though not always, the subjects are obese. Muscular activity is retarded. The reparative processes of the body are defective and wounds or fractures heal slowly. The activity of the red bone marrow is often depressed, leading to a condition of anemia.

Thyroid deficiency appearing at any age from intrauterine stage to adult years gives rise to the same general picture. The adult form of the disease is

*Meticulous writers prefer the designation, *childhood myxedema*, holding that the true *cretinism* of continental writers represents a special degenerative condition technically different from that of simple thyroid deficiency.

known as *myxedema.* In this the clinical manifestations of the disorder are, of course, modified by the fact that the patient has attained full stature and sexual maturity. Growth defects are not apparent, but disturbances of sex functions such as impotence, sterility and menstrual irregularity are important clinical manifestations. Various other clinical data bearing on thyroid deficiency are cited by Marine[96] and by Means.[100] Myxedema may occur spontaneously from thyroid atrophy, or it may follow the surgical removal of the gland. In the latter case "cachexia strumipriva" or "operative myxedema" is applied to the condition. Except in the mildest cases the signs are very characteristic. The skin is dry and thick, with a deposition of a fluid of high protein content in

Fig. 351.—Cretin, nineteen years old. The treatment with thyroid extract was started too late to be of benefit. (Patient of Dr. S. J. Webster.)

the subcutaneous tissues. (Ord introduced the term myxedema on the assumption that the edematous condition of the skin is due to the local accumulation of mucin.)

Quite distinct from the above described conditions of hypothyroidism are those produced by an excess of thyroid hormone in the blood; namely, *hyperthyroidism.* Hyperthyroidism may occur with or without ophthalmic symptoms, and it is rather widely believed that there are two distinct conditions associated with hyperfunction of the thyroid: (1) *Simple or "pure" hyperthyroidism* due to an adenomatous state of the gland (toxic adenoma) and which is associated

with symptoms that can be duplicated in animals by the administration of excessive doses of thyroid extract or of thyroxine; (2) *Exophthalmic goiter,* characterized in addition by ocular symptoms that cannot be accounted for by the action of the thyroid principle. The details of the symptoms and especially the nervous manifestations in the two conditions are said to differ significantly. The thyroid gland in exophthalmic goiter is enlarged, sometimes in one lobe only; it is hard and pulpy, and on auscultation a murmur is heard. Histologically the gland presents a picture of hyperplasia, that is to say, the vesicles have a deficiency of colloid material; their epithelium is columnar in type and their walls are thrown into folds.

Until recently the *control* of the thyroid gland has presented a largely unsolved problem. The evidence that clinical hyperthyroidism may be induced by emotional shock suggests that the gland is directly or indirectly under nervous control but numerous attempts to determine the secretory innervation of the thyroid have not given consistent results. The fact that a thyroid graft (which

A. *B.*

Fig. 352.—*A,* case of myxedema; *B,* same after seven months' treatment. (After Tigerstedt.)

is of course devoid of innervation) can maintain a thyroidectomized animal in good health indicates that nervous control is not primarily essential. This latter evidence suggests that the activity of the gland is in considerable measure determined by the composition of the blood. There is substantial evidence, as Collip,[30] Friedgood[45] and others have shown, that a major factor in the control of the gland is a special hormone—the *thyreotropic*—from the anterior lobe of the pituitary body. Following hypophysectomy or removal of the anterior lobe alone, a depression of the thyroid early ensues. Conversely, by the use of a special extract from the anterior pituitary, the thyroid can be thrown into a state of increased activity such as exists in clinical hyperthyroidism as seen in man. To what extent thyroid activity depends upon direct nervous or metabolic stimulation and to what extent such influences express themselves via the pituitary remains largely for further research to determine. It is probable that the reactions of the thyroid to such conditions as puberty, menstruation and pregnancy are mediated through the pituitary.

Various other interglandular relationships involving the thyroid have been postulated but the status of these is, in general, somewhat uncertain. The literature has been reviewed by Marine.[96]

In conclusion, the question may be asked, what is the adaptive significance of the thyroid? The fact that it is found as an active secreting structure in all vertebrates above the lowest fishes indicates that it subserves an important function. On the other hand, insects and various other invertebrates live efficiently without benefit of thyroid hormone. Even in the higher animals a considerable amount of biological activity persists in the absence of the hormone. It would seem well within the possibilities of evolution that an optimal degree of intrinsic tissue activity might have arisen without dependence upon this hormone. The fundamental biological significance of the gland seems to lie in its function of aiding the organism in adaptation to changing environment—external and internal—such as climatic alterations, dietary changes and such epochs of special stress as puberty and pregnancy. It is correspondingly probable that further studies of thyroid physiology will be most fruitful if addressed to these primary relationships.

CHAPTER LXXI

THE PARATHYROID GLANDS

The parathyroid glands appear first in the scale of life at the amphibian level. Embryologically they originate from tissue of the third branchial arch. It is a matter of ultimate physiological importance that the thymus also originates from this (and the fourth arch as well) whence it comes about that in its migration to its final position it is likely to carry parathyroid tissue with it. This explains why in certain animals aberrant parathyroids are frequently found as inclusions in the thymus. In the cat it has been reported to occur in 50 per cent of the subjects. Even in man parathyroid inclusions in the thymus have been reported by Brewer[20] to be of far more frequent occurrence than was formerly thought. Furthermore, the glands vary in their location in different animals even when normally placed. Thus a source of error difficult to control is present in experimentation. It is not improbable that much of the earlier work in which complete parathyroid extirpation was believed to have been achieved represented only various degrees of glandular deficiency. Thus may be explained various otherwise puzzling contradictions in the literature.

The fact that the parathyroid contains two distinct types of cells supports a surmise that the gland has at least two different functions. But only one is yet clearly known. Which cell type contributes the activity to the potent extract that is now in use is not known.

Parathyroids were first described by Remak in 1855 though credit for their discovery commonly goes to Sandström, who published (1880) a clear description of them but regarded them as merely displaced, undeveloped, fragments of thyroid tissue. Their independent functional importance was demonstrated by Gley in 1881. In an earlier paragraph mention was made of the confusion that arose in the earlier experimental work on the thyroid because of failure to appreciate the part played by the parathyroids.

Important evidence as to the functional significance of these glands can be obtained by studying the effects of their destruction, either experimentally in animals or inadvertently in thyroid operations in man. Under such conditions, commonly within less than a day, the blood calcium drops about one-third and tenseness with sensations of tingling or numbness begins to appear. Fine tremors can be detected in the muscles of the fingers or elsewhere. The tension increases and painful muscular cramps begin to appear in different parts of the body. At this time the blood calcium has further decreased to about 6 mg. per 100 ml. (the normal level is 10 mg.). Convulsive movements occur involving either single limbs or the entire body. Laryngeal spasm and marked cyanosis may arise requiring vigorous therapy to forestall immediate death. These manifestations mark the condition known as *tetany*. It may occur any time from sixteen hours to six days after the operation (Aub[12]). The tetany is due in part to increased excitability of the muscular tissue itself and in part to that of the nervous system. Since each muscular contraction multiplies the stimuli with which the sensitized nervous system is bombarded, a vicious circle is set up.

An important clinical manifestation of parathyroid deficiency is *chronic latent tetany*. Although the patient is free of the grosser manifestations, he

shows a general tendency to irritability, and by special tests, such as pressure or tapping over motor nerve trunks, muscle spasms can be induced. A lowered threshold to galvanic stimulation of nerve trunks is also demonstrable.

A subacute type of parathyroid deficiency has been reported by Shannon[124] who recorded the cases of eight children who developed convulsions followed by mental depression and irrational speech. The condition progressed to acute maniacal excitement with screaming, fighting, and tearing of the clothes. Terrifying dreams were common. In six of the cases the use of parathyroid extract was followed by relief of the symptoms. Whether day to day variation in placidity or irritability of normal subjects is in any measure determined by fluctuations in parathyroid secretion has not been determined.

The mechanism by which parathyroid deficiency produces increased neuromuscular irritability has not been adequately determined. It is not unlikely that the phenomenon is related to changes in cell permeability resulting from shifts in the titer of circulating calcium.

The foregoing manifestations are those most commonly seen. In other instances—in cats often and in dogs sometimes—instead of tetany a severe *progressive lethargy* supervenes. This is likely to be associated with marked malnutrition and early death. The factors which determine the kind of reaction are not well known.

The functional condition of the thyroid seems to play a part in the reactions to parathyroidectomy. With age, susceptibility to parathyroid deficiency decreases, and the symptoms become more easily controlled. The symptoms are made more severe by pregnancy, lactation, constipation, muscular exertion, infections, and fever.

The symptoms following parathyroid destruction are suggestively similar to those produced by strychnine, the toxin of rabies or of the tetanus bacillus. Although the symptoms are chiefly ascribed to disturbances of calcium metabolism there is some indirect evidence that intoxication may play a part. Koch,[78] and later, other investigators have isolated from the urine of animals in experimental tetany the toxic body, methyl guanidine. Injections of this substance into normal animals cause a marked increase of irritability which at least superficially resembles that of parathyroid deficiency. Unlike the latter condition, however, it is not relieved by treatment with calcium or parathyroid extracts. That intoxication of some sort plays an important rôle is indicated by the observations of Dragstedt,[36] who has found that withholding meat from the diet, preventing constipation, and administering lactose with copious quantities of fluid may serve to keep an animal in excellent health despite the destruction of all known parathyroid tissue. Such measures may be superior to the use of parathyroid extract in the treatment of clinical parathyroid deficiency.

The part that may be played in the tetanic manifestations by the acid-base balance of the body is not clear, though various writers have regarded it as important. By the administration of alkaline salts or, in susceptible subjects, by rapid breathing and by excessive vomiting, it is possible to obtain convulsions. This fact must be taken into account when clinical tetany suspected of being of parathyroid origin is encountered. Actually, in parathyroid tetany the body fluids are not usually unduly alkaline and at the height of the convulsions may shift definitely toward the acid side.

It is generally agreed that the most important factor in the production of parathyroid tetany is a disturbance of calcium metabolism and of the calcium-phosphorus equilibrium. The normal calcium titer in the blood is about 10 mg. per 100 ml. and that of inorganic phosphorus, 5 mg. That removal of the glands causes a marked fall in the calcium content of the blood has been frequently confirmed in a variety of animals. Conversely, parathyroid convulsions can be quickly checked by the injection of calcium salts. Calcium gluconate lends itself particularly well to this purpose though calcium chloride can be used if care be taken to prevent its escape into the tissue about the vein into which the injection is made. Luckhardt showed that if calcium salts are given by mouth in adequate amounts, parathyroidectomized animals can be kept alive and in good health indefinitely. After a time internal re-adjustment may take place rendering continuation of treatment unnecessary.[36]

How the parathyroid secretion functions in maintaining calcium equilibrium presents a difficult problem. It appears to act in part by controlling the absorption of calcium from the alimentary tract. The excretion of calcium is lessened by administering the parathyroid hormone, whereas destruction of the glands results in a severalfold increase of the excretion. The chief influence, however, of the hormone, so far as immediate influences are concerned, is regulation of the transference of calcium between the skeleton and the blood. Since thyroxine also has an important influence in the mobilization of stored calcium, it can be used as a useful adjunct in the treatment of parathyroid deficiency. Large doses of vitamin D are also useful to the same end.

This latter fact, together with the similarity between the symptoms of parathyroid deficiency and those of rickets indicates that there is a significant relationship between vitamin D and the parathyroid hormone, but details of the relationship are not clear. According to Aub[12] vitamin D when given in large enough amounts exerts much the same effects on the body as do parathyroid extracts. It raises the calcium level in blood; but, unlike the extracts, it also increases absorption of calcium from the intestinal tract. Vitamin D has certain advantages; it is effective by mouth whereas parathyroid extract must be given parenterally, and its effects are persistent. It has the disadvantage that it requires days to bring the subject under its influence, while parathyroid extract requires but a few hours.

A picture the converse to that of parathyroid deficiency can arise from hyperfunction of the glands or can be produced by the injection of parathyroid extracts. The method of producing potent preparations was discovered almost simultaneously by Hanson, by Berman, and by Collip in 1923-1924. The method is relatively simple; it consists in boiling the fresh parathyroid tissue in weak hydrochloric acid, neutralizing, and filtering. Rather pure extracts are now commercially available, but the hormone itself has not been isolated. Since the potency of the extracts is destroyed by peptic digestion, it is probable that the active principle is of protein nature.

The most striking effect of administering parathyroid extract is a marked increase in the blood calcium. The extract is most effective when administered by vein and somewhat less so when given intramuscularly. Oral administration is not effective. Following a single injection, blood calcium gradually rises for several hours, then gradually falls. If enough is given to increase the blood calcium level by half, vomiting may occur and the blood may show an increased

tendency to clot. With massive dosage the calcium titer may increase to as much as 23 mg. per 100 ml., often with fatal results during the second or third day. The viscosity of the blood rises to a point at which efficient circulation becomes impossible. Various species of animals differ in their susceptibility, dogs being highly responsive and rabbits almost indifferent as regards these deleterious effects. Associated with the increased blood calcium is a decrease in the inorganic phosphorus. Both elements are excreted in abnormal amounts, hence if the injections are long continued the body supply becomes markedly depleted. The trabeculae of the bones are first drawn upon and then the shafts. At the same time the activity of the osteoblasts is increased, and the blood phosphatase rises. A disadvantage in the clinical use of parathyroid extract in complete parathyroid deficiency is that the subjects gradually lose their reactivity to it; the dosage has to be frequently increased, and finally a stage is reached in which no dosage is adequate to forestall a fatal issue.

Although parathyroid deficiency has been known clinically for years, the opposite condition, *hyperparathyroidism,* has only recently become recognized as a definite disease. The disorder arises insidiously and becomes chronically progressive. It is characterized by early weakness and by pains in the bones, with increasing debility that ultimately brings the patient to a bedridden state. As the bones lose minerals they become softened and liable to fracture. The destructive process is irregularly distributed with a tendency to cyst formation. A certain degree of restorative activity accompanies the destructive processes with replacement of bone substance by connective tissue. The final condition in the skeleton is known as *osteitis fibrosa cystica,* a condition marked by generalized osteoporosis, cysts, and giant cell tumors. Anemia and hypotonia of both skeletal and smooth muscle are characteristic. Depression of excitability to the electric current is common. The blood calcium ranges abnormally high and phosphorus low. Both elements are excreted in excessive amounts. Deposits of calcium are likely to occur in the soft tissues and especially in the kidneys. Correlated with the resulting renal irritation is a tendency to polyuria with consequent polydipsia. Ultimately there may occur sufficient destruction of kidney tissue to lead to contraction and depressed function. As a result, nitrogenous waste products tend to accumulate in the body fluids.

As regards the *control* of parathyroid secretion little is known. Recent work indicates that the glands are in some measure controlled by a hormone from the anterior lobe of the pituitary. In certain hypophyseal tumors hyperplasia of the parathyroids has been detected; a similar condition has been produced by the injection of anterior pituitary extract. For the suggested hormone the designation, *"parathyrotropic"* has been offered, but there is some evidence that the principle having the activity mentioned is the "prolactin" of Riddle (see chapter on Hypophysis).

Presumably the parathyroid secretion is adaptively related to changes in environmental conditions and especially to diet, but details are lacking. Apparently the chief general significance of the parathyroid hormone is the facilitation of mobilization of calcium and phosphorus salts which, in their stored form, are chemically rather inert.

For further details regarding parathyroid physiology the excellent reviews by Thomson and Collip,[137] and by Dragstedt[36] may be consulted.

CHAPTER LXXII

THE ADRENAL GLANDS*

The mammalian adrenal is made up of two distinct parts, the *cortex* and the *medulla,* the functions of which are apparently independent. A frequently used synonym for the glands is "suprarenal," but since the structures lie *above* the kidneys only in the few animals that assume the erect posture, the term is largely a misnomer. In many vertebrates below the mammalian group the cortex and the medulla are represented by separate organs, the *interrenal bodies* and the *chromophil bodies,* respectively. Interrenal bodies are found as low in the scale of life as the cyclostome fishes. Chromophil tissue has been identified in several invertebrates—notably in the abdominal ganglia of leeches. For further details of the comparative anatomy of the adrenals the book by Grollman[53] may be consulted.

Embryologically the adrenals of man arise in close association with the primitive sex glands with which they are more or less associated functionally throughout life. That they play an important role in prenatal existence is suggested by their precocious formation; in the third month of fetal life they are the most prominent structures within the body cavity. At birth they are about a third as large as the kidneys but in early infancy a relatively thick zone lying between the medulla and the outer part of the cortex undergoes involution with consequent reduction in the size of the total gland. At this period hemorrhages within the gland take place with relative ease. The portion of the gland that thus undergoes absorption has recently been designated by Grollman[53] as the "androgenic zone." He regards it as a third independent entity having only the function implied in the name. According to Broster and Vines[23] the androgenic tissue can be differentiated histologically by its affinity for fuchsin dye.

Accessory cortical bodies have been described in various mammals and these are of importance to the experimental physiologist because, in operations designed to produce complete cortical deficiency they may be left behind and by their hypertrophy defeat the purpose of the experiment or lead to false conclusions. *Accessory chromophil bodies* are also of wide occurrence. The *carotid body* is of chromophil nature, and there are small masses of chromophil cells, the *paraganglia,* associated with the sympathetic nerve ganglia. The extent to which the accessory chromophil tissue may serve to complicate physiological experiments is somewhat uncertain, but satisfactory evidence of their having any vital role has not been adduced.

The size of the adrenals varies with a number of conditions. In some species they are proportionately ten times as large as in others. They become hypertrophic in fevers, after exposure to heat or to cold, in inanition, and in poor health. The adrenals of the wild rat are larger than those of the domesticated variety. In some species they are larger in females than in males. They also enlarge during pregnancy and retain the enlargement during the lactation period. In some species they enlarge in both sexes during the breeding season.

*This chapter deals chiefly with the adrenal cortex. The adrenal medulla, although a definite endocrine organ, may be considered, on embryological and physiological grounds, to be a part of the sympathetic division of the autonomic nervous system. It has been considered in Chapter XVI.

The hypertrophy under these various conditions is largely or entirely restricted to the cortical portion. It is probable that the hypertrophy is in considerable measure due to antecedent changes in the anterior pituitary.

ADRENAL DEFICIENCY

The adrenals were clearly described by Eustachius as early as 1563. Over the succeeding years various picturesque theories as to their functions were evolved,[69] but it was not until 1855 when their relationship to Addison's disease was discovered that their physiological significance began to be apprehended. This disorder, which is due to destructive lesions of the cortex, may be described in Addison's own classic words:[3] "The leading and characteristic features of the morbid state to which I would direct attention are, anaemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change of colour in the skin, occurring in connection with a diseased condition of the 'suprarenal capsules.' . . . This singular discoloration usually increases with the advance of the disease; the anaemia, languor, failure of appetite, and feebleness of the heart, become aggravated; . . . . the body wastes . . . . the pulse becomes smaller and weaker; and without any special complaint of pain or uneasiness the patient at length gradually sinks and expires."

Despite the assiduous efforts of many investigators since the time of Addison his contribution remains the most significant in the history of adrenal research. Relatively little that is fundamental in the syndrome of adrenal failure has since been added to the gross picture.

Shortly after the publication of Addison's monograph, Brown-Séquard[24] essayed to reproduce the syndrome experimentally. He removed the adrenals from dogs, cats, rabbits, and guinea pigs with results seemingly confirmatory of Addison's observations—marked prostration and early death. When shortly afterward, however, it was independently shown by two other investigators that rats were able to survive in good health after what appeared to be complete extirpation of the adrenals, confidence in Brown-Séquard's results was undermined.

Research on the glands then languished for forty years until interest was revived by the work of Oliver and Schäfer[105] in 1894. These investigators reported the discovery that adrenal extracts are characterized by "an extraordinary effect upon the tone of the heart and arteries, transcending that of any known drug." In the meanwhile the picture of adrenal deficiency had been shown to include marked weakness of the heartbeat and low blood pressure. These factors could well account for the accompanying prostration. Oliver and Schäfer's new observations therefore appeared convincingly to supplement the findings of Brown-Séquard and to indicate as the vital function of the adrenals that of sustaining cardiovascular activity (tonus). For the next two or three decades the "tonus theory" appealed to most physiologists as a satisfactory explanation of the *raison d'être* of the glands. Researches largely turned therefore to studies on the physiology of the medullary secretion, *adrenalin*. The outstanding addition to knowledge at this time was the fact that this substance has a highly selective influence on effectors innervated by the sympathetic nervous system (Elliot[38]). So intimate is the relationship that the physiology of the adrenal medulla can advantageously be discussed with that of the sym-

pathetic division of the autonomic nervous system (see Chapter XVI). For details regarding the effects of adrenalin on the various tissues and organs consult Sharpey-Schäfer.[125]

Early in the twentieth century, evidence began to appear which rendered the tonus theory increasingly untenable. Although the morphological pathology of Addison's disease remained a matter of dispute, evidence was gradually accumulating that it is destruction of the cortex rather than of the medulla that is etiologically important. The primacy of the cortex was largely determined by Biedl[16] when he discovered that in the skate, in which form the medullary and cortical homologues are anatomically separate, destruction of the interrenal bodies, leaving the chromophil bodies intact, results in death. One skate, in which a small proportion of the interrenal body was left, survived without symptoms. Several investigators, among them Biedl, then attempted to destroy either the cortex or the medulla in mammals, leaving the other moiety more or less intact. The accumulating weight of the evidence thus derived was supportive of Biedl's work on the skate. Mammals were frequently found to survive partial adrenal extirpation when only cortical tissue could be demonstrated in the persisting parts of the glands. From such experiments it appeared that health can be sustained in animals possessing no medullary tissue and as little as one-eighth of the normal amount of cortex. Certain investigators continued to hold, however, that the presence of extramedullary chromophil tissue in the animals vitiated such experiments.

In further attempts, then, to settle the functional significance of the medulla, attention was turned to a study of the properties of adrenalin in relationship to the "tonus" of sympathetically innervated effectors. It was noted that when the blood supply of the adrenals was cut off, thus suspending the secretion of adrenalin, no detectable disturbance in blood pressure occurred for a matter of hours, whereas the pressor influence of adrenalin is notably evanescent. If the function of the adrenals were to keep the circulatory system under "tonic" stimulation by secreted adrenalin the sudden withdrawal of this substance should have led to an immediate fall of blood pressure. The tonus theory in its simple form thus became untenable. The possibility remained, however, that adrenalin might have a more slowly acting influence leading to the same general end: it might play a necessary role in preserving the responsivity of the sympathetic nervous system. Researches by Hoskins and various collaborators[67] brought forth several facts incompatible with the tonus theory in either guise. It was found that when adrenalin was slowly infused by vein into animals showing effects of acute adrenal deficiency, there was no improvement in sympathetic reactivity. Indeed, in a considerable proportion of the experimental animals, the infusions served to depress the irritability. It was also noted that if adrenalin in high dilution were administered to a normal animal the effect was not, as theory demanded, to increase the blood pressure but to lower it. The depressor effect was shown to be due largely to selective vasodilatation in the arterioles of the skeletal muscles. It was also discovered that the motor functions of the gastrointestinal tract were suspended by adrenalin in smaller doses than those necessary to produce a minimal effect upon blood pressure. For further information regarding the physiology of the adrenal medulla the reader is referred to the chapter on the Autonomic Nervous System (Chapter XVI).

Adrenal Cortical Deficiency.—The remainder of this discussion will be devoted to the physiology of the adrenal cortex. Since studies aiming to elucidate this function are largely based, directly or indirectly, upon extirpation experiments, the results of these become a matter of paramount importance. Adrenal extirpations in the pre-antiseptic days were, of course, hazardous and for a considerable period after the publication of Brown-Séquard's work[24] it was a moot question whether the fatal outcome of such operations was due to an interference with gland function or to the surgical hazards. With the introduction of asepsis and the improvement of technique the matter became clarified. There is now no doubt that complete removal of all cortical tissue is a fatal operation. The time of survival can be extended by meticulous attention to operative technique and by utilizing a two-stage operation, allowing a few days to intervene between removal of the first and the second gland. Under such conditions the survival period, in the various laboratory animals, ranges from a few days to a few weeks. Ordinarily, if accessory cortical bodies are overlooked or if fragments of cortex are inadvertently left behind, the animal survives indefinitely because of the hypertrophy of these structures. Occasionally, however, the animal goes into a chronic, progressive, partial adrenal insufficiency from which it ultimately dies. Grollman emphasizes this phenomenon as offering a probable explanation for the apparent efficacy of inferior adrenal extracts in prolonging life.

Animals lacking their adrenals are highly sensitive to traumatic injury or hemorrhage. The survival period is significantly prolonged by keeping the animals in a warm environment. In general, young animals survive for shorter periods than adults, a fact probably correlated with their more rapid metabolic processes. Initial good nutrition and general good health are assets in surviving the operation. Expeditious operating with consequent shortening of the time of anesthesia prolongs the survival period, while excitement and exercise as well as high protein diets shorten it. There is some, but not concordant, evidence that pregnancy lengthens the survival period. Estrus, which leads to increased bodily activity, shortens the period whereas castration, which has the opposite effect, lengthens it. Any sort of infection or intoxication which depletes the vitality shortens the period. Presumably, all the conditions mentioned have their counterparts in patients suffering from Addison's disease.

In untreated, fatal adrenal insufficiency, the picture shown by various animals is roughly the same. After a brief stage of recovery from the operation the animal appears to be normal in every way. The wounds promptly start to heal and the subjects show a normal alertness and desire for food and drink. The blood pressure is normal and the chemical constituents of the blood preserve their normal relationships. But within a few days symptoms of insufficiency begin. The animal becomes apathetic, refuses food and not infrequently vomits bile or blood-stained material. Watery or bloody diarrhea is often seen. Muscular movements become slow and uncertain and not infrequently twitching or even convulsions supervene; a characteristic disturbance of gait often develops because of predominant weakness of the hind legs. Eventually, the animal becomes prostrated and will respond to only intensive stimulation. In warm-blooded animals the body temperature gradually falls, the skin becoming cold and the mucous membranes pale. In the acute phase respiration is rapid and then gradually becomes slow. Anuria may supervene. The animal finally falls into coma with respiratory paralysis from which death occurs while the heart is still beating.

During the first part of the postoperative period the arterial blood pressure is approximately normal but during the last two or three days of life it falls off at an increasing rate until, shortly before death, it is approximately half the normal level. The body temperature and the rate of oxygen consumption follow a somewhat similar course. The body weight begins to recede quite early and

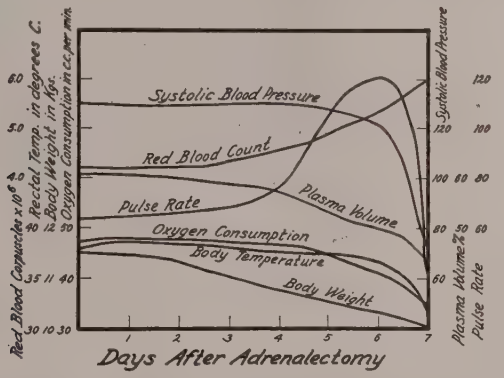


Fig. 353.—Changes in various physiological functions in adrenal insufficiency. The curves represent composite records of results obtained on dogs adrenalectomized in stages. The animals received no therapy during the period of study and died seven days following the removal of the second gland. (From Grollman: *The Adrenals*, Baltimore, 1936, The Williams and Wilkins Company.)

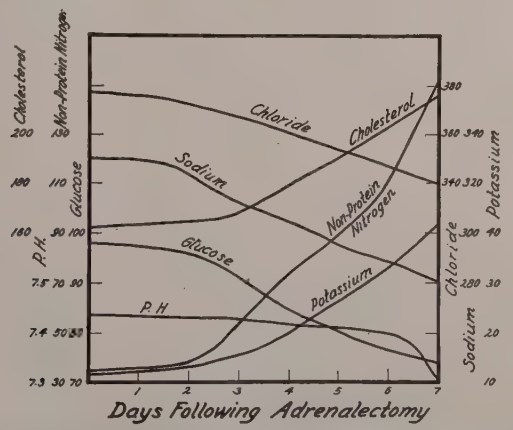


Fig. 354.—Changes in the blood chemistry in adrenal insufficiency. The curves represent composite records of results obtained on dogs adrenalectomized in stages. No therapy was given during the period of study and the animals died seven days following the removal of the second gland. With the exception of the pH, values are expressed in milligrams per 100 c.c. (ml.). (From Grollman: *The Adrenals*, Baltimore, 1936, The Williams and Wilkins Company.)

continues to diminish, partly because of the anorexia and partly because of dehydration. Accompanying the dehydration, and perhaps because of it, the plasma volume decreases and the red-blood-cell count goes up. The changes are indicated in Fig. 353. Similar increases are noted in the blood cholesterol and the blood potassium with even more marked increase in the nonprotein nitrogen,

which may reach values five or six times the normal. The sodium and the chloride content of the blood falls as commonly does also the blood sugar (Fig. 354).

The precise cause of death in adrenal deficiency has been much debated. Hartman[62] believes that the cause is a generalized interference with cellular metabolism. Britton[21] has laid special stress on disturbance of sugar metabolism as being fundamental, while Swingle[135] has claimed that the central feature is a shocklike inability of the organism to maintain the normal volume of circulating fluid. Considerable stress is laid by some authors on the rise in blood potassium and the resulting potassium-sodium imbalance that follows adrenal extirpation.[53] Restoring the balance by the administration of sodium chloride together with sodium citrate (to counteract the tendency to acidosis which develops) has an ameliorating influence in subjects with Addison's disease as well as in experimental adrenal deficiency. Kendall has reported that with no other treatment than administration of these salts two dogs have survived in complete health for a period of months without any cortical tissue whatever.

Cortical Extracts.—When it became apparent, early in the present century, that it is the cortex which is the vitally necessary part of the gland, many efforts were made to secure the cortical hormone in extracts sufficiently potent to prevent the syndrome of adrenal deficiency. Occasional claims of some degree of success were made but failed of satisfactory substantiation. As late as 1924 Sharpey-Schäfer[125] wrote: "There is no clear evidence that any kind of active . . . . substance is produced by the adrenal cortex." The first reported successes that attracted wide attention were those of Rogoff and Stewart[115] and of Hartman, MacArthur and Hartman[65] in 1927. Both reports were in the form of brief preliminary notes in which it was stated that extracts had been secured which significantly prolonged life in dogs or cats from which both adrenals had been removed. Stewart and Rogoff used saline solution and glycerin as extracting media and Hartman used a sodium chloride extract from which the proteins were removed by isoelectric precipitation. For the vital hormone Hartman proposed the name *cortin.* Subsequent work has shown that none of these methods possesses more than minimal efficacy but the two reports were very significant for the stimulus they afforded to further studies. The first investigators to report a method of preparing extracts sufficient to maintain indefinitely the lives of adrenalectomized animals were Swingle and Pfiffner.[136] This was in 1930. Two months later Hartman and Brownell[63] reported an equally successful method. At the present time several methods are available, each of which yields extract capable of prolonging indefinitely the lives of animals devoid of cortical tissue and of significantly ameliorating the symptoms of Addison's disease (Harrow and Sherwin[61]). Of these the process of Swingle and Pfiffner has been most widely used, but Grollman claims unusual simplicity for his method.

Although several crystalline products have been obtained from cortical tissue it cannot be said with certainty that any one represents the vital hormone. Cevitamic acid (vitamin C) which occurs in fairly high concentration in the adrenal cortex is apparently devoid of hormonal influence.

Whether the adrenal cortex forms more than one hormone and whether any available extract represents the entire potency of this structure are moot questions. Hartman[64] has reported that cortin does not support lactation, but that it is possible to derive another cortical extract, *cortilactin,* which does. Hoskins and Freeman[71] have found that a simple glycerin extract of adrenal cortex has

a significant influence in raising the blood pressure in a considerable proportion of human subjects, an effect not obtainable under comparable conditions from cortin or similar preparations. They believe that it represents a principle different from the so-called "vital" hormone. It may be this pressor principle, formed in excess, that gives rise to a condition of chronic hypertension which is occasionally seen in man and has not otherwise been accounted for (Barr[14]). It may be the absence of this principle from other types of cortical extracts that accounts for their relative inefficacy in sustaining the blood pressure of subjects with Addison's disease. Larrain, Roberts, and Kunde[80] have discovered that if minced cortical tissue is dialyzed against distilled water it continues for weeks to give off a powerful pressor substance which is not adrenalin. The production of this material is apparently due to enzymatic action, since it is promptly suspended when cyanide is added to the gland substance. Whether it represents a hormone or a chemical artifact is not known.

The availability of potent cortical extracts has made it possible, by subjecting animals to adrenalectomy and then partially supplying their hormonal need, to create a condition of *experimental chronic adrenal deficiency*—a condition that more or less closely simulates Addison's disease. The result is a general loss of vitality manifested especially by a lack of spontaneous activity and increasing malnutrition with almost complete loss of body fat. In young animals growth is retarded or suspended in accordance with the severity of the deficiency. Growth capacity can be restored by cortical extract, a fact that some investigators have utilized for the assay of extracts. The sex functions are depressed or obliterated; male animals become impotent and females remain in a state of permanent diestrus. Chronic deficiency renders the subjects less than normally resistant to environmental stresses and they succumb easily to intercurrent disease. Lesions are sluggish in healing. The animals are reported to be particularly susceptible to vitamin deficiency. By gradually decreasing the supply of extract the condition can be brought to a terminal stage closely resembling that of Addison's disease. A noteworthy exception, however, is that it has not been possible to reproduce with certainty the pigmentation that is characteristic of this disorder in man.

For the most part the *visceral changes* noted in animals dead of adrenal deficiency are simply those of "chronic passive congestion," a marked hyperemia of the visceral organs—stomach, intestines, liver, spleen, kidneys, pancreas, thymus, and hypophysis. Lesions of the gastric mucosa are characteristic; they include hemorrhage, superficial erosions, and true ulcers. Degenerative changes in the liver are common, a fact of interest in connection with the disturbance of carbohydrate metabolism characteristic of the disorder. Especially noteworthy are hypertrophic changes in the lymphatic system and in the pancreas. Despite the fact that cardiovascular weakness is a prominent symptom during life, the heart and blood vessels are found to be approximately normal. Altogether, postmortem studies have added little to our knowledge of the functional significance of the adrenals.

The relationship of the adrenals to the *respiratory metabolism,* despite a great deal of study, is not entirely clear. Immediately after adrenalectomy a mild fever associated with increased "basal metabolism" is frequently observed. Marine has laid stress upon this phenomenon as indicative of an intimate relationship between the adrenals and the thyroid, the hyperthermia being

ascribed to sudden escape of the thyroid from adrenal control. The increase, however, is soon succeeded by a substantial depression of the rate of oxygen consumption. In the terminal stages of adrenal insufficiency the rate may be less than half the normal value. A similar depression of the body temperature is seen.

FUNCTIONAL RELATIONSHIPS OF ADRENALS TO OTHER ENDOCRINE GLANDS

Adrenal-Pituitary Relationship.—Of recent years much stress has been laid on the controlling influence of the *anterior pituitary* upon the adrenal cortex. The relationship seems to be reciprocal. In dogs maintained on minimal doses of adrenal cortical hormone for periods of one hundred days and then allowed to die of adrenal insufficiency, Grollman and Firor[54] found changes in the pituitary similar to those reported in patients dying of Addison's disease. There was congestion of the gland and a marked decrease in the basophilic cells. Such animals develop a clinical picture essentially like that of hypophyseal cachexia. The physiological deficiencies manifested by such animals are not remedied by treatment with cortical hormone but are in some measure corrected by treatment with anterior pituitary extracts. Young animals suffering from early adrenal deficiency respond to cortical extract by an increase in the growth rate, but it is possible by long-continued subacute deficiency to set up a condition in which little growth response can be obtained. In such conditions the normal growth rate can be restored by the use of anterior pituitary extract. The importance of the pituitary-adrenal relationship is also shown by the fact that the depression in the reproductive system that occurs in chronic adrenal deficiency can be corrected more successfully by pituitary than by cortical extracts.

The Influence of the Adrenals Upon Pancreatic Diabetes.—An interglandular relationship demanding consideration is that between the adrenals and the *pancreas*. Long[85] has observed that experimental diabetes mellitus can be ameliorated by adrenalectomy. The effect is similar to that produced by hypophysectomy (see pages 765 and 767). Long's work was made possible by the availability of potent extracts of the adrenal cortex. These permitted the study of totally depancreatized and adrenalectomized cats over survival periods of several weeks. It was found, for example, that the average survival of adrenalectomized-depancreatized cats was nearly three times as long as that of cats in which only the pancreas had been removed. But the mere extension of the survival period is of far less significance than the fact that the double ablation prevents the rise in the excretion of glucose and nitrogen to the high levels characteristic of the pancreatectomized animal. Further, the typical ketonuria with acidosis fails to develop. Table CVII shows this and compares the results with those obtained in the hypophysectomized-depancreatized animal. Long has secured evidence that the effect of adrenalectomy on the course of pancreatic diabetes is not due to removal of the adrenal medulla. When this operation is performed in partially depancreatized rats the glycosuria temporarily disappears only to return to its initial level; if then total adrenalectomy is carried out, the glycosuria disappears permanently. It was also found that the innervation of the adrenals is not concerned, for cats with denervated glands rapidly succumb to the effects of pancreatectomy. It

can be concluded that the amelioration of diabetes mellitus by adrenalectomy is the result of removal of one or more hormones of adrenal cortical origin.

Relationship of the Adrenals to the Gonads.—That a relationship exists between the adrenals and the *sex organs* has been clearly recognized since Bulloch and Sequeira[26] described a condition now commonly known as the *adrenogenital syndrome.* A few years later Glynn[52] described at length the condition as it occurs in women and children. The salient fact is that hypertrophy of the adrenal cortex and precocious development of the sex organs occasionally take place coincidentally. In some instances mere accentuation of the sexual attributes is noted but usually in females there is also a more or less well-marked transformation toward the masculine type. The disorder occurs about five times as frequently in girls as in boys. In the juvenile form the onset is usually within the first two years of life. According to Grollman[53] the condition is marked by hyperplasia of the androgenic zone of the cortex and this leads to the appearance of such secondary male characteristics as increased

TABLE CVII

SURVIVAL AND THE EXCRETION DURING FASTING OF GLUCOSE, NITROGEN, AND ACETONE BY VARIOUS CATS (FROM LONG[85])

TYPE OF ANIMAL	NUMBER		SURVIVAL	URINE				BLOOD SUGAR
				GLUCOSE	NITROGEN	ACETONE	$\frac{D}{N}$	
			days	g/k/d*	g/k/d*	mg/k/d*		mg./100 ml.
Depancreatized	22	Average	5.3	3.2	1.3	116	2.7	347
		Range	2-12	1.6-6.4	0.8-2.2	28-275		212-788
Hypophysectomized-Depancreatized	19	Average	22.0	0.4	0.7	5	0.6	190
		Range	8-85	0.0-1.5	0.3-0.9	0-27		16-355
Adrenalectomized-Depancreatized	18	Average	14.0	0.6	0.6	13	1.0	186
		Range	5-28	0.0-1.6	0.3-0.9	3-48		13-362

*Signifies Gm. or mg. per kg. per day.

muscular development, deepening of the voice, luxurious growth of hair (pubic and sometimes facial), hypertrophy of the vulvar structures, and enlargement of the clitoris to simulate a small penis. At times the ovaries and uterus share in the enlargement, but menstruation does not occur. The picture in boys is comparable; the secondary sex characteristics become accentuated, but the testes remain immature. The term "infant Hercules" is often applied to boys who have suffered this mishap. The condition differs from true precocious puberty that may result from tumors of the pineal or of the primary gonads in that it is only the secondary characteristics which are affected. Since the cortical involvement is frequently a malignant neoplasm that metastasizes freely it is important that surgical intervention be instituted early in the development of the syndrome. The surgeon, however, should examine both glands because occasionally that opposite the one affected is rudimentary or absent.

When the adrenogenital syndrome arises in adult women the condition is usually called *adrenal virilism.* It occurs most often either during the early years of adolescence or at the climacteric, but cases have been reported in the intermediate years. The picture is one of regression of the feminine secondary

sex attributes and of a transformation toward the masculine, similar to that described in the juvenile form. The vagina, mons veneris, labia, and mammae atrophy, and regressive changes in the ovaries have been described; menstruation ceases. The pubic hair pattern assumes the masculine form and excessive hair growth occurs, particularly on the face, chest, and thighs. The larynx also assumes masculine proportions. In the early stages of the disease marked adiposity of the upper half of the body is common. Later, cachexia and progressive asthenia occur. When only one of the two adrenals is involved, surgical treatment may be largely or entirely curative.

The condition of adrenal virilism is closely similar to, if not identical with, the *pituitary basophilism* described by Cushing. There is a rare type of neoplasm of the ovary, *arrhenoblastoma,* which also gives a similar clinical picture, a fact which suggests that certain accessory ovarian cells and those of the androgenic portion of the adrenal cortex are functionally identical. A characteristic case of arrhenoblastoma has recently been described by Baldwin and Gafford.[13]

Rarely, a condition, the converse of virilism, namely a transformation to the feminine type, occurs in males in association with tumors of the adrenal cortex. Such a case described by Lisser[84] was characterized especially by enlargement of the breasts and lactation. In one such case surgical removal of the adrenal tumor resulted in regression of the breasts and resumption of normal masculine sex functioning. Obviously, the occurrence of such instances, rare though they be, necessitates hesitancy in ascribing purely masculinizing potency to the adrenal cortex; the term *androgenic* tissue may have to be supplemented.

The relationships between the adrenals and the reproductive functions have been further discussed by Looney.[86]

There is a condition known as *pseudohermaphroditism* that has been somewhat plausibly ascribed to overactivity of the adrenal cortex during the prenatal stage of existence. In this condition the uterus and primary gonads are indubitably feminine but the external genitalia are largely of the masculine type. In some of the more recently reported cases hyperplastic changes in the adrenal cortex have been seen.

The *total biological significance* of the adrenal glands cannot at the present time be assayed. The medulla seemingly has an important function of aiding in adaptation to conditions that demand vigorous neuromuscular activity. In this it supplements sympathetic activity (see Chapter XVI). That the cortex has important functions may be assumed from its occurrence throughout the vertebrate group and from the fatal results of its destruction. The fact that it is proportionately very large during the prenatal period suggests that it may have an important part in the regulation of early growth and development. Its precise connection with reproduction has not yet been clearly elucidated, though its relationships with the pituitary and the gonads clearly indicate important regulatory functions. Its relationship to carbohydrate and fat metabolism and to the process of lactation demands further investigation. It seems probable that the cortex secretes more than a single hormone and that no extract that has hitherto been described represents the total potency of the structure.

CHAPTER LXXIII

THE HYPOPHYSIS OR PITUITARY GLAND

References to the pituitary as a distinct anatomical structure occur in medical writings as early as the time of Galen. Vesalius gave it the name "pituitaria" thus perpetuating a long-held misapprehension of its function, that of secreting a pharyngeal lubricant (*pituita*, mucus). This secretion was supposed to pass through the interstices of the cribriform plate of the ethmoid bone into the nasal cavity. After Conrad Schneider overthrew this idea in 1660 the gland came to be regarded as merely a vestigial organ.

Various aberrations of the growth processes now known to be due to pituitary abnormalities have long been recognized. Giants and dwarfs have engaged the folk imagination from time immemorial. The actual relationship of the pituitary to bodily overgrowth first came to be appreciated in connection with acromegaly, a modified type of gigantism. A case was reported by Verga in 1864 in which abnormality of the pituitary gland was recognized. Klebs thirty years later treated the subject of acromegaly in a monograph; the excessive size of the pituitary was emphasized, but the question whether the glandular enlargement was to be regarded as the cause or merely as a part of the bodily overgrowth was left undecided. To Pierre Marie (1886) is usually given the credit for having finally determined the causal relationship of the pituitary to acromegaly.

The reader is referred to textbooks of histology for a detailed description of the various components of the pituitary gland. It must suffice here to give a mere outline of the organ as it appears in the mammal. The reader should turn to page 189 for an outline of the major divisions and subdivisions of the hypophysis. These are also indicated in Fig. 355. Two main divisions are distinguished. The *neurohypophysis* is derived from the infundibular process of the diencephalon, while the three subdivisions of the *adenohypophysis* represent differentiations of Rathke's pouch of buccal ectoderm. The buccal derivatives are the pars distalis, pars intermedia and pars tuberalis. Usually the term *anterior lobe* refers only to the pars distalis. The term *posterior lobe* is sometimes used to describe all of the gland lying behind the intraglandular cleft (the residual lumen of Rathke's pouch) and thus includes the pars intermedia as well as the pars neuralis, but more commonly it refers to the neural portion alone. The position of the pars tuberalis varies somewhat in different species; it usually forms a collar around the upper part of the pituitary stalk and spreads to a greater or lesser extent over the ventral suface of the tuber cinereum. Its functions are not understood.

The parts of the pituitary possess different histological features. The pars nervosa is composed of neuroglia, unmyelinated nerve fibers and certain peculiar neuroglia-like cells which have been termed pituicytes (Bucy). The cells of the adenohypophysis are definitely of the secretory type. In the anterior lobe (pars distalis) two types of cells, the *chromophiles* and *chromophobes* can usually be recognized. On the basis of staining reactions the chromophilic cells are divisible into *acidophiles* and *basophiles*. The chromophobic cells may be mother structures for the two chromophilic elements. The cells of the pars intermedia are nongranular basophilic cells, but they differ from the basophilic elements of the anterior lobe. The intraglandular cleft tends to be filled by a colloid material which certain writers have supposed to be a secretory product of the pars intermedia. In some species, especially the primates, cells from this portion of the gland invade the pars neuralis. The pars tuberalis consists of cells arranged in acini which are sometimes filled with a colloid-like material. Histologically, the pars tuberalis differs from all other parts of the pituitary; the cells are usually faintly basophilic.

The pituitary gland of mammals receives its blood chiefly from a number of small arteries which arise from the circle of Willis and accompany the stalk. Wislocki and King[143] have recently shown that in the monkey the anterior lobe is supplied by afferent portal veins as well as by arteries and that the two unite to form the sinusoids which are characteristic of this portion of the gland. The efferent venous drainage of the pituitary as a whole is by veins which enter the cavernous sinus. According to Wislocki and King the portal system of veins originates in capillaries in the stalk. Previously Popa and Fielding[109] had claimed that in the human an extensive set of portal veins carries blood from the entire pituitary into the nervous tissue of the hypothalamus, but Wislocki and King were unable to find any evidence of this system in the monkey.

The nerve supply of the hypophysis has two origins. Sympathetic fibers from the superior cervical ganglia have been traced into the anterior lobe (Dandy), but up to the present no clear-cut function has been ascribed to them. Of apparently greater functional importance are the unmyelinated fibers which reach the gland from the hypothalamus by way of the pituitary stalk (see Chapter XVII). The histological evidence available shows quite clearly that they supply the pars nervosa and, to a less extent, the pars intermedia. The work of Ranson and his collaborators[113, 110] has shown that these fibers are active in connection with the elaboration of the antidiuretic hormone of the posterior lobe. Brooks[22] has secured evidence which demonstrates that in the rabbit ovulation depends on the activation of the anterior lobe by nerve fibers which course in the stalk.

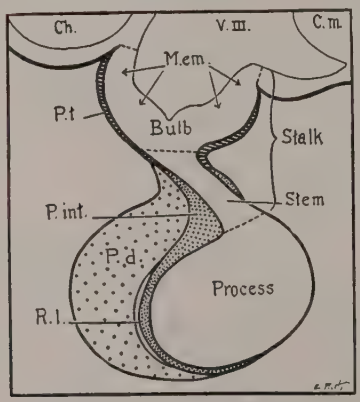


Fig. 355.—Diagram of the hypophysis of a monkey (*Macaca mulatta*) showing the subdivisions of the gland.

Bulb, infundibular "bulb" or "infundibulum" of Tilney; *Ch*, optic chiasma; *C. m.*, corpus mammillaria; *M. em.*, median eminence; *P. d.*, pars distalis (anterior lobe); *P. t.*, pars tuberalis (shaded); *P. int.*, pars intermedia (fine stippling); *Process*, infundibular process (neural lobe); *R. l.*, residual lumen (intraglandular cleft); *Stem*, infundibular stem; *Stalk*, neural stalk together with mantle of lobus glandularis constituting the hypophysial stalk; *V. III.*, third ventricle. (From Rioch and Wislocki in *The Hypothalamus*, A. Research Nerv. & Ment. Dis. Proc. 20: 3, 1940, Williams and Wilkins Company.)

The hypophysis appeared early in vertebrate evolution. In the lowest fishes it is represented by an open gland discharging directly into the pharynx. Also in the human embryo the gland has an early origin. By the fourth week of intra-uterine life the pharyngeal and neural components have already made contact. By the eighth month the blood supply of the gland has become rich and secreted material is being deposited in the cleft. In the ninth month the final cell types are determined. As to how early the gland begins to function in man little information is available, but in the pig embryo it yields a growth-promoting extract when the animal is at about half the birth-length. It is at this stage too that thyroxine can first be detected in the thyroid gland. In

amphibia it is possible to remove the pituitary at an early larval stage. The operation results in interference with development; the adrenals, the gonads and the thyroid fail to reach normal proportions and, in consequence, metamorphosis from the larval to the adult form fails to take place. It seems probable that the human pituitary plays a significant rôle in development from the early fetal months on. During pregnancy the hypophysis of the mother hypertrophies, a fact suggesting that the fetus obtains part of its growth hormone through the maternal circulation. The growth impulse, however derived, persists for a short time after birth even if the pituitary gland is removed. After this early period, however, the operation promptly and permanently renders growth impossible except as missing hormones are artificially supplied.

From the physiological point of view the hypophysis must be considered in relation to its various components. As sources of potent extracts the anterior and posterior lobes are distinctly different. There is also evidence that the pars intermedia subserves an independent function. The function of regulation of growth can be rather definitely ascribed to the acidophilic cells of the anterior lobe. The differential function of the basophils is less clearly known, but Zeckwer[147] has obtained some evidence suggesting that they produce hormones which regulate the thyroid, adrenal and sex glands. That an active extract can be secured from the neural lobe seems at first sight anomalous, for it is made up largely of neuroglia tissue and does not appear to contain definite glandular cells. Many investigators have concluded that its pharmacological activity is derived from cells of the pars intermedia or anterior lobe. There is, however, excellent evidence that the active substances (antidiuretic, pressor, and oxytocic) in question are actually produced by elements in the neurohypophysis. For example, they disappear from the gland when the neural lobe atrophies as a result of cutting the pituitary stalk, a procedure which does not cause atrophy of the pars intermedia and pars distalis.

A major difficulty in the elucidation of the functions of the pituitary is the intimate relation between the gland and the adjacent parts of the brain. Injuries to the hypothalamic area, whether produced experimentally, by accident, or by neoplastic invasion, have been shown to lead to such disturbances as obesity, polyuria and abnormalities of carbohydrate metabolism (see Chapter XVII). Similar disorders can be produced experimentally by injuries to the hypophysis. Experimentally it is extremely difficult to remove all of the gland without injuring the hypothalamus. In many animals the position of the pars tuberalis is such that at least some of it remains after the contents of the sella turcica have been completely removed. It is possible that this fact accounts for some of the discordant results which have been reported. Unfortunately scarcely anything is known of the functional properties of this portion of the gland. It has been suggested that the hypothalamus and the hypophysis constitute a functional system similar to that of the adrenal medulla and the sympathetic nervous system (see Chapter XVII).

THE NEURAL LOBE AND THE PARS INTERMEDIA

Knowledge of the functions of the posterior lobe, which consists of pars intermedia and neural lobe, has been difficult to secure. The classic first approach to experimental endocrine physiology, namely, study of the effects of extirpation of the structure in question, has yielded relatively little information regarding the

normal functions of the posterior lobe. Here a clean-cut surgical extirpation without significant injury to adjacent structures is most difficult—perhaps impossible. When an ablation has been confined very largely to the posterior lobe the one outstanding result is an increase in the amount of water ingested and excreted. This experimental polyuria with polydipsia is in every way similar to clinical cases of *diabetes insipidus* in many of which evidence of pituitary involvement is found. In both the experimental and the clinical forms of this disorder the polyuria can be controlled by administration of extracts of the posterior lobe of the pituitary. This fact has led to the belief that diabetes insipidus is due to a diminished output of an antidiuretic hormone from the posterior pituitary. Today the bulk of evidence favors this view. It also appears that the continued production of the antidiuretic substance depends upon the integrity of the innervation of the secretory cells by a group of fibers which arise in the hypothalamus, chiefly in the supraoptic nuclei. The cells which elaborate the antidiuretic hormone are found not only in the neural lobe but also in the pituitary stalk and even in the median eminence. Their distribution appears to differ in different species. Ranson and his collaborators[110] have shown that interruption of the fibers of the hypothalamico-hypophysial system (see page 192) leads to a permanent experimental diabetes insipidus with atrophy of the neural lobe. Richter,[111] working on rats, and Ingram and Fisher,[74] who used cats in their experiments, found that at least a part of the anterior lobe must be left to obtain a permanent polyuria after ablation of the neural lobe. The inference is that the pars distalis elaborates a diuretic hormone. It is a fact that complete hypophysectomies rarely produce permanent polyurias. It has been found that the disturbance in water balance does not develop if only a small fraction of the neurohypophysis is left intact.

The literature on the subject of the relation of the pituitary and the hypothalamus to water balance presents a most confusing picture. It has been frequently claimed that a hypothalamic injury is essential for the production of polyuria and even that such injury leads to a permanent polyuria after complete removal of the pituitary (Camus and Roussy; Bailey and Bremer). On the basis of the work of Ranson and his collaborators[43, 110] on cats and monkeys one may conclude that hypothalamic injuries are effective because they destroy the tonically active nerve supply of the posterior lobe, thus stopping the elaboration of the antidiuretic hormone. Richter's results suggest that the polyuria is dependent on the unantagonized action of a diuretic substance given off by the anterior lobe. Certain findings, however, appear to contradict these interpretations of the matter. It has been claimed that in the rabbit and monkey complete section of the stalk does not influence the urinary output in any permanent manner. It now seems reasonable to interpret these negative results as being due to the fact that unless the stalk section is very high it fails to disconnect the nerve supply of many of the cells which secrete the antidiuretic hormone. As indicated above, these may be distributed in the stalk and median eminence as well as in the neural lobe.

In connection with their classic studies on adrenal extracts in 1894 Oliver and Schäfer[106] discovered that the injection of pituitary extract causes a marked rise in blood pressure. Subsequent researches showed that it was the posterior lobe that contributed this property (Howell, 1898). Supplementary to this observation is Cushing's report[32] that localized tumor growth which compresses the pituitary stalk in man and thus presumably stops the discharge of posterior-lobe secretion may result in low blood pressure. The case is cited of a twenty-three-year-old victim of such a growth in whom the systolic pressure was only 60 mm. Hg.

In 1909 Dale[34] reported the discovery that injection of posterior-lobe extract causes a marked contraction of the uterus—as it does of smooth muscle generally. Abel and his associates[1] have devoted much study to the chemistry and pharmacology of posterior lobe extracts. They have succeeded in deriving a tartrate so potent as to cause marked contraction of uterine muscle when applied in concentration of 1:15,000,000,000 or less than one grain in a thousand tons of fluid. This substance possesses pressor, oxytocic (uterus-stimulating) and antidiuretic properties. Kamm and his associates[76] have separated from postpituitary extracts two fractions, "*pitressin*" and "*pitocin,*" in a highly purified state. In experimental animals pitressin has a marked stimulatory influence on blood pressure and respiration, and it sharply checks the secretion of urine. It has also a certain melanophore-expanding activity, but this according to Geiling[49] decreases with purification and is due to a separate principle elaborated by the cells of the pars intermedia. Pitocin has mainly an oxytocic activity. Both pitocin and pitressin cause hyperglycemia and counteract the effects of insulin.

In the human subject therapeutic injections of either total posterior lobe extract or of pitressin cause a marked pallor of the skin but little or no significant rise of blood pressure. There is a brief fall in pulse rate, in oxygen consumption and heart-output which is followed by a more prolonged rise. The decreased cardiac output results in an accumulation of catabolites associated with the decreased oxygen consumption which is followed by a compensatory secondary increase. In experiments in which cardiac effects are eliminated, larger doses of the extract produce a sharp rise of blood pressure but on repetition of the injections the effect is soon lost.

In the earlier experiments with posterior lobe extracts it was noted that the immediate effect in experimental animals was an increase of urine flow. Accordingly, in the older literature the extracts figured as "diuretic." Subsequent work, however, has shown that therapeutic doses of either the post-pituitary extract or of pitressin have a marked antidiuretic effect. As already mentioned, this property is of use clinically in the treatment of diabetes insipidus, in which condition a troublesome urinary output that may reach ten or more liters per day can readily be held within approximately normal limits by injections once or twice daily. The action is, at least mainly, on the kidney itself and is probably due to an increased reabsorption of water by tubule cells. McQuarrie[93] has recently reported several cases in which pitressin injections caused temporary water-retention which was followed by a marked diuresis that more than compensated for the initial antidiuretic effect. He was thus able to bring about marked reduction in an existing edema. He surmised that this secondary reaction might be due to induced secretion of an anterior-lobe diuretic principle.

The oxytocic effects of post-pituitary extracts are modified by various factors such as species, phase of the sex cycle, pregnancy itself, and the stage of pregnancy. During the early phases of pregnancy in human cases the uterus fails to react to pitocin but does respond to small doses of pitressin. Later in gestation it becomes reactive to pitocin and the parturient uterus is highly reactive. In the puerperium the reaction is again lost. The principal clinical use of posterior lobe extract is in the stimulation of uterine contractions during childbirth, and more especially, to bring about such contraction as will check post-

partum hemorrhage or bring to completion an arrested abortion. It is of some utility in the induction of labor but must be used with caution. It is effective when administered intranasally and this route is often advisable, permitting, as it does, the cautious building up of the dosage to the effective point. Overdosage may be disastrous. As a smooth-muscle stimulant the drug is also occasionally of practical use in overcoming atony of the intestines or bladder.

From the foregoing evidence it may be rather plausibly surmised that the posterior lobe of the pituitary has important physiologic functions in the control of the circulation and of smooth-muscle tonus generally, in the process of parturition, in water metabolism, and possibly in fat metabolism. It must be emphasized, however, that the various active principles do not necessarily represent true hormones—they may be chemical artifacts—and that their existence in the cerebrospinal fluid, into which it is commonly postulated that they are discharged, has not been satisfactorily proved. The paucity of evidence of physiological disturbances following destruction of the posterior lobe reenforces such doubt as one may entertain. If the pharmacological evidence is interpreted as indicative of the existence of hormone functions, it must be assumed that the body has at its command effective compensatory mechanisms that can be brought into play when the hormone secretion is interfered with.

Zondek[144] is a proponent of the view that the pars intermedia secretes a hormone which he calls "*intermedin.*" This substance is commonly found in extracts of the posterior lobe. It is notable chiefly for its effect in bringing about expansion of the melanophores in amphibia and certain fish. This reaction has been used in the quantitative assay of the material. Intermedin has not as yet been used at all extensively in clinical practice but such evidence as is available indicates that it is of use in the treatment of diabetes insipidus. It is said to differ in its action from pitressin in that it checks only water output whereas pitressin reduces both the fluid and the sodium-chloride excretion. The manner of its action is not known.

THE PARS DISTALIS OR ANTERIOR LOBE

Control of Growth.—Studies of the clinical manifestations associated with structural abnormalities of the pituitary have thrown considerable light upon the functions of the anterior lobe. Previous mention was made of the influence upon body structure of enlargement of this portion of the hypophysis. When the glandular overactivity antedates puberty, the whole body shares in the exuberant growth, and *gigantism* results. When it takes place after puberty, increase in the length of long bones is no longer possible, but other structures not thus circumscribed show generalized hypertrophy. Thus arises splanchnomegaly and distorting overgrowth of such structures as the inferior maxilla, the nose, the ears, the glabellar prominences and the hands and feet. At times the hebetic closing of the proliferative zones of the long bones intervenes in the overgrowth process with the result that what began as gigantism is completed as *acromegaly*.

Folk lore recounts the occurrence of very large giants but seldom does the height authentically much exceed eight feet. A few of the tallest giants on record are indicated in Table CVIII.

TABLE CVIII

(AFTER SCHERESCHEWSKY[122])

GIANT	AUTHOR REPORTING	HEIGHT
Kayanus		9.2 ft.
Winkelmeyer	Virchow	9.0 ft.
Krav	Kiari	8.9 ft.
Konstantin	Dufreny	8.4 ft.
Scotchman	Freulich	8.4 ft.
Austrian	Topiner	8.3 ft.

Rarely in gigantism and acromegaly the anterior lobe is found to be of approximately normal size but in such cases relative overdevelopment of the acidophilic cells is commonly evident. The weight of available evidence indicates that it is from these cells that the growth-promoting *(somatotropic)* hormone is derived.

A. *B.*

Fig. 356.—*A*, the appearance before the onset of acromegalic symptoms; *B*, the appearance after seventeen years of the disease. (After Campbell Geddes.)

Lee[81] and others have shown that extirpation of the anterior lobe results in a profound alteration of the metabolic processes. The work suggests that the growth hormone has a relationship to protein metabolism somewhat comparable with the relationship of insulin to carbohydrate metabolism. In the absence of the growth factor the assimilation and storage of protein are interfered with. The defect can be compensated by the administration of a suitably prepared anterior lobe extract. The hormone in this case is either a globulin or is of such nature that it appears with the globulin fraction in purified extracts. Riddle[114] has raised the question, however, whether the so-called "growth hormone" represents a single entity or whether it is a composite of other fractions that have individually different functions than the promotion of growth. At any rate no one has yet succeeded in producing a growth fraction that is entirely free of effects ascribable to other fractions. The inherent complexities of protein chemistry render the problem difficult of solution.

The fact that the growth fraction is no more abundant in the anterior lobes of calves than of adult cattle suggests that the somatotropic hormone functions throughout life, but of its functions in adult years we have little knowledge beyond the suggestion from the work of Lee that it may continue to serve as a regulator of protein metabolism.

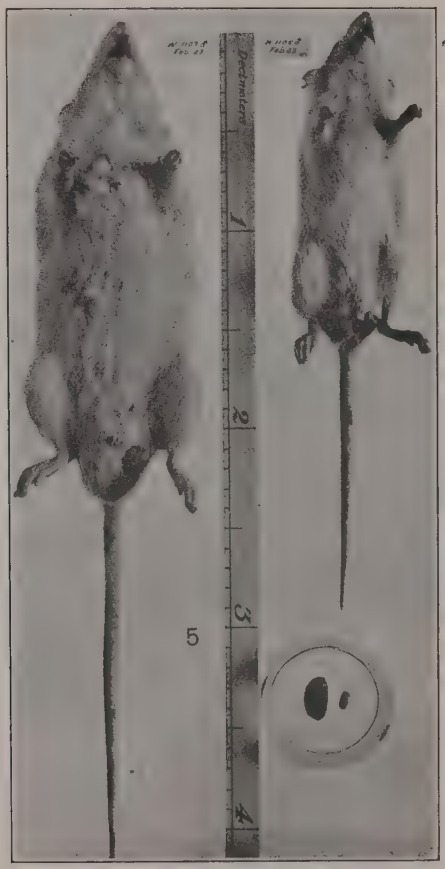


Fig. 357.—Photograph of a hypophysectomized rat and its litter mate control. The hypophysectomy was done at the age of thirty-six days; weight, 96 Gm. The photograph was taken eighty-nine days later. A testis removed from each animal at this time is also shown. (After P. E. Smith.)

Failure of development of the anterior lobe results in the condition known as *dwarfism*. The first major surgical contribution to the physiology of the pituitary was the proof by Aschner and by Cushing that experimental dwarfism can readily be produced by destruction of the anterior lobe. The type of human dwarfism due to deficient production of the somatotropic hormone has been designated by Erdheim as *nanosomia pituitaria*. Several other types

are known of which the most interesting, from an endocrine viewpoint, is that due to hypothyroidism. Evans[40] believes it probable that all forms of dwarfism are directly due to inadequate pituitary function but that this inadequacy may be brought about by several antecedent factors. Experimental dwarfism is frequently associated with obesity, but this is usually ascribed to injury of the hypothalamus incident to the operation. The final proof that the dwarfism is due to deprivation of growth hormone rather than merely injury of trophic structures in the nervous system has been afforded by Smith[132] and others who have been able to restore the growth impulse either by the implantation of anterior lobe grafts or by the injection of anterior lobe extract (Figs. 358 and 359). The latter is now being used to some extent clinically in the treatment of dwarfism, but so far with only moderate success (Shelton[128]).

Fig. 358.—Photographs of two female rats about four hundred days old. The rat on the right received daily intraperitoneal injections of anterior pituitary extract. Its litter mate sister on the left was untreated. (After Evans.)

The classification of human dwarfism at the present time is somewhat unsatisfactory. The difficulty is due in part to the fact that the defective growth may or may not be associated with failure of sexual development or function. Some dwarfs have normal adult proportions but more often those of childhood are retained, the upper length of the body exceeding the lower. In some cases of dwarfism a peculiar senile manifestation (*progeria*) is seen. Thus the individual may become senescent at 25 and suffer an early death.

Another clinical manifestation of pituitary deficiency in which the somatotropic factor is involved is a peculiar cachectic condition reported by Simmonds in 1914. *Simmonds' disease* is marked by a rapidly wasting state which is found at autopsy to be associated with destruction or sclerosis of the pituitary. In this case all parts of the gland seemed to be involved. According to Evans, Simmonds' cachexia is not due primarily to deficiency of growth hormone because when the condition is set up experimentally by pituitary destruction in animals, it cannot be corrected with purified growth extract but can be relieved by more crude preparations. The course of Simmonds' disease may be rapidly

progressive to a fatal issue or death may be postponed for years. The patient ages prematurely as is indicated by such manifestations as atrophy of the skin and loss of hair. The emaciation affects the body tissues generally and gives rise to progressively increasing weakness and fatigability. Lack of appetite is a common and stubborn symptom. Increased thirst and a voluminous urine output are frequently seen in the earlier phases of the disorder, but later tend spontaneously to be corrected. The oxygen-consumption rate falls well below normal and a moderate decrease in the number of erythrocytes occurs. Often carbohydrate metabolism is disturbed. The genital organs frequently show atrophy; depression of the sex functions is an invariable and usually an early symptom. These clinical observations have obvious connotations regarding the physiology of the pituitary.

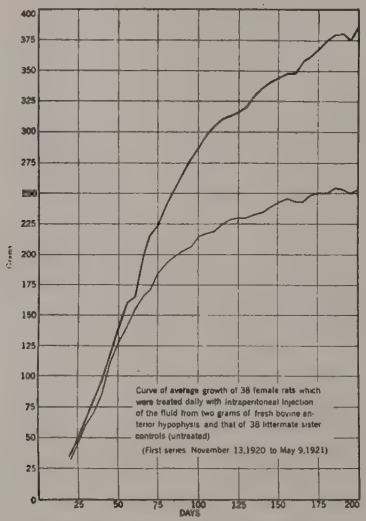


Fig. 359.—Curve of average growth of 38 female rats which were treated daily with intraperitoneal injections of anterior lobe extract; and that of 38 litter mate sister controls (untreated). (After Evans.)

The extent to which functional deficiency aside from Simmonds' disease may arise in later years of life is not known. Presumably the gland shares with other organs of the body a liability to such failure from the operation of fatigue, malnutrition, infection and what not. So complex are the functions now ascribable to pituitary secretions that the clinical manifestations of deficiency of the gland would presumably be multiform. Among the symptoms that have been vaguely ascribed to such pituitary depression are lowered oxygen consumption, malnutrition, weakness, generalized hypometabolism, eosinophilia, augmented uric acid titre of the blood, depression in the sex field and changes of disposition.

Gonadotropic Effects.—The first experimental evidence indicating a relation between the pituitary and the reproductive system was obtained by Crowe, Cushing and Homans in 1910. In the course of a study of the effects of

complete and partial hypophysectomies they found that when adult dogs were deprived of all but a fragment of the anterior lobe reversive sexual changes set in; the females failed to come in heat and the males exhibited no signs of sexual activity. When similar operations were performed on puppies a persistence of sexual infantilism resulted. Two years later Aschner also found that hypophysectomy causes an atrophy of the reproductive system. Since that time these results have been abundantly confirmed. The precise nature and origin of this hypophysial influence were not clearly shown until 1926 when it was independently discovered by P. E. Smith[132] and by Zondek and Aschheim[145] that implants of anterior lobe substance into immature rats and mice would bring about precocious sexual maturity within a period of about four days. In this way

Fig. 360.—Simmonds' disease in a woman aged fifty-three years. (Silver: Arch. Int. Med. 51: 175, 1933.)

it was conclusively shown that the anterior lobe maintains the activity of the gonads and through the internal secretions of these organs influences the other parts of the reproductive system.

The literature on this topic has already become highly complex. It has been authoritatively reviewed by Smith.[131] In the case of the female the elementary facts are that along with the typical growth of follicles, ovulation, and the formation of corpora lutea, there occurs as a result of implanting anterior lobe also a lutein-transformation of the walls of many ovum-containing follicles. The weight of the evidence at the present time is to the effect that two hormones are involved. One has been called the "follicle-stimulating hormone" (F. S. H.) and the other the "luteinizing hormone" (L. H.). Both are referred to as *"gonadotropic"* principles.

As regards the follicle-stimulator, the term is rather ill-chosen in that the male gonad is also influenced. In both sexes it is the germ cells proper that are affected, hence Smith proposes that it be designated as the *gametokinetic* hormone. The luteinizer, on the other hand, appears to act predominantly on the connective-tissue derivatives, the theca cells of the ovaries and the interstitial cells of the testes. In addition to their appearance in anterior-pituitary extracts, gonadotropic substances have been discovered in human blood and urine during pregnancy, after ovariectomy and at the menopause, in certain tumors of the reproductive organs, and, in smaller amounts, in the blood and urine of men and women during the normal reproductive period. A gonadotropic substance can be separated in relatively large amounts from the blood serum of pregnant mares and in small amounts from the blood of some other animals after castration. Some of these gonadotropic principles are derived from the anterior pituitary and some from the chorionic tissues of the placenta. A still different source is a peculiar tumor of the female, arrhenoblastoma, which

Fig. 361.—*Above:* Ovaries of litter mate control rat; *below:* ovaries of rat after twelve implantations of fresh rat pituitary gland. (After Collip.)

causes a marked masculinizing effect. The interrelation among, and the physiologic significance of, these various gonadotropic factors present difficult problems that are as yet only partly solved.

Several methods of fractionating anterior lobe extracts for gonadotropic factors are available. Hisaw and Fevold,[66] among others, have devoted special attention to separating the follicle-stimulating and the luteinizing principles. A fraction has been secured by the use of which pure follicular growth can be obtained in hypophysectomized rats, in young rabbits and, with limited treatment, in immature rats. In the latter form, however, corpus luteum formation is set up after several days treatment—a result that is ascribed to secretion of luteinizer from the animal's own hypophysis. In immature monkeys both the pituitary "F. S. H." and extract of urine of castrated animals give pure follicular growth. It is believed that these latter two substances are identical. Shedlovsky and his collaborators[126] have isolated the luteinizing factor in apparently pure form. It has the properties of a globulin. Its molec-

ular weight is about 90,000 and its isoelectric point pH 7.45. It was found to be a necessary adjunct to pure follicle-stimulator in the production of estrus in young hypophysectomized rats.

The action of castrate-urine "F. S. H." in hypophysectomized males is of special interest. The seminiferous epithelium of their atrophied testes shows a marked response, spermatids and even spermatozoa being produced, with little or no change in the interstitial tissue. Conversely, there can be obtained from pregnancy urine a fraction, possibly of pituitary origin, which produces not only luteinization in females but extensive hypertrophy of the interstitial tissues in males. Overactivity of the interstitial tissues is commonly associated with marked development of such secondary sex structures as the prostate and seminal vesicles.

Fig. 362.—Photographs showing the effects of the urinary gonadotropic substances on the ovary of hypophysectomized immature rats. *5* is the ovary of an untreated animal twenty days after hypophysectomy. *6* is from another immature rat twenty-five days after hypophysectomy; during the ten days preceding removal of the ovary the animal had received injections of an extract of human pregnancy urine (chiefly luteinizing substance). Note formation of luteinlike cells and absence of follicular growth. *7* is the ovary of an immature rat twenty days after hypophysectomy. The animal had received for five days an extract of urine from a castrate woman (follicle-stimulating substance). Note formation of many normal follicles with but slight indication of luteinization. (From Smith and Engle: J. Pediatrics, 5: 163, 1934.)

These topics will be further discussed in a subsequent section dealing with the physiology of reproduction.

The Lactogenic Factor.—Among other effects of anterior lobe pituitary deficiency is inability of a mother to secrete milk. Several investigators have obtained pituitary extracts which stimulate lactation. Riddle[113] succeeded in isolating the lactogenic factor in a degree of purity sufficient to permit a demonstration of its distinctiveness from the growth and gonad-

stimulating factors. He has called it, "*prolactin.*" Turner[138] who has also done important work on the subject, prefers to call it "*galactin.*" All the successful methods of preparing this fraction involve extraction of anterior-lobe tissue, precipitation in an aqueous medium by adjusting the pH to the isoelectric point and repeated washing of the precipitate. Salt-free preparations at a pH of 8.0 withstand boiling for an hour with little loss of potency. The active substance is completely destroyed by tryptic digestion—a fact which suggests that it, like other anterior pituitary hormones, is of a protein nature. There are four known responses to the administration of prolactin. These are setting up of lactation in mammals, growth of the crop gland in pigeons, initiation of broodiness in fowl, and marked diminution in the size of the active gonads of adult pigeons or fowl. The hormone apparently has no influence upon the growth or development of the mammary gland but serves only to set it into secretory activity after it has previously been prepared by the action of the ovarian hormones. A plausible theory is that during pregnancy mammary gland maturation is brought about by these hormones, which are especially active at that time, but that the action of the lactogenic factor is suppressed by ovarian or placental hormones that are known to be produced in large amounts during this period. At parturition the production of the suppressing factor ceases, thus liberating the secretion of the prolactin from the pituitary, whereupon the breasts begin active functioning. This theory is supported by the fact that treatment of male animals with ovarian hormones may bring about development and hypertrophy of the mammary glands after which the administration of prolactin leads to milk secretion.

Prolactin has also a marked influence upon certain instinctual reactions. Wiesner and Sheard[142] were able to bring about a marked development of the maternal instincts in virgin rats by the use of crude anterior pituitary extract. Riddle has extended their observations, using a purified preparation. Under its influence the rat develops a strong propensity to "mother" not only infant rats but also mice or squabs. She builds elaborate nests for them and hovers about them with all the solicitude of a veritable mother. The induction of broodiness and clucking in fowl presumably represents another manifestation of the same influence.

Prolactin has as yet been little used clinically, but Kurzrok[79] has treated with this substance a group of women in whom lactation had remained inadequate up to the sixth day after the birth of their infants. In most cases the milk production was significantly increased. In several women whose secretion was apparently normal prolactin produced no detectable effect.

The Thyreotropic Factor.—That a relationship between the hypophysis and the *thyroid* exists has long been known. A half century ago Rogowitsch[116] noted an enlargement of the pituitaries of dogs and rabbits following thyroidectomy. The observation has often been confirmed. Conversely, destruction of the pituitary has been shown by several observers to result in atrophy or failure of development of the thyroid. In tadpoles this atrophy prevents metamorphosis into the adult form but the ability can be restored by pituitary implants. In the rat, as shown by Smith,[130] hypophysectomy not only causes atrophy of the thyroid gland as shown by histologic observations, but also reduces the oxygen consumption rate as much as 35 per cent—the same amount as that produced by thyroidectomy. In man a similar reduction in the metabolic

rate has been shown to characterize Simmonds' disease of which thyroid atrophy is also characteristic. Conversely, thyroid hypertrophy can readily be set up by the administration of suitable anterior lobe extracts. The evidence strongly supports the belief that this latter effect is due to the action of a distinct principle, the *thyreotropic* hormone. Collip[30] and others have obtained a thyreotropic principle nearly or quite free from growth or sex-promoting activity. Friedgood[45] has pointed out the close resemblance between the condition produced by administration of thyreotropic hormone and that of exophthalmic goiter in man. The action of the thyreotropic hormone seems to be of limited duration, the hypertrophic effect in the thyroid with its accompanying elevation of the basal metabolic rate being followed by thyroid regression and fall of the rate even below normal. This latter effect may, however, be due to contaminating material in the extract rather than to the hormone itself. These observations obviously suggest that clinical hypothyroidism (myxedema) can arise not only from primary thyroid disease but as a secondary reaction to disorder of the pituitary.

The Adrenotropic Factor.—Almost as marked as the thyroid atrophy following pituitary extirpation is regression of the adrenal cortex. This regression can likewise be overcome by the administration of pituitary implants. In acromegaly and other clinical conditions associated with overactivity of the hypophysis hypertrophy of the adrenal cortex is of frequent occurrence. Presumably such observations indicate the existence of another anterior pituitary function; namely, that of secreting *adrenotropic* hormone. The separation of a fraction having a purely adrenotropic effect has been difficult, but Collip[29] has obtained a preparation which can be given in dosage adequate to cause marked adrenal hypertrophy without producing detectable influence on the thyroid.

Further evidence of a functional relationship between the hypophysis and the adrenals is seen in the condition of "pituitary basophilic adenoma" described by Cushing.[33] In this disorder a series of bodily changes arise that closely resemble, if they are not identical with, those of an "adreno-genital syndrome" which sometimes follows overactivity of the adrenal cortex. This topic has been discussed in the chapter dealing with the adrenals.

It is at least theoretically possible that Addison's disease, which is immediately due to destruction of the adrenal cortex, may actually have its initial cause in failure of the adrenotropic secretion of the pituitary. Supporting this possibility are two cases of that disorder mentioned by Collip in whom marked improvement occurred following the use of adrenotropic extract.

The Parathyreotropic Factor.—Clinical evidence for an interrelationship between the pituitary and the parathyroid glands has been reported by several observers. The association of parathyroid adenomas with tumors of the hypophysis is suggestive of such a relationship. It is claimed, too, that the urine of patients having hyperplasia of the parathyroids can be used to produce experimental hyperplasia in the same glands of rabbits. Riddle, however, has noted that similar effects can be brought about with prolactin and suggests that the so-called *parathyreotropic* hormone is no other than the lactation-producing principle.

Influence on Carbohydrate and Fat Metabolism.—What was already recognized as a highly complex situation—the endocrinology of the pituitary—was

rendered still more complicated when Houssay[72] in 1930-1931 reported the remarkable observation that removal of the hypophysis strikingly lessens the manifestations of diabetes in pancreatectomized animals. This procedure would seem to amount to superimposing the condition of Simmonds' disease upon that of diabetes. While neither disorder actually cures the other, the symptoms of each in considerable measure cancel those of the other and thus temporarily conserve the health of the experimental animal. In the dog the period of survival after the double operation may extend to six or nine months. That a relationship exists between the anterior pituitary and carbohydrate metabolism had previously been surmised from the frequent observation of glycosuria and hyperglycemia or even of frank diabetes in acromegaly, but the primacy of the association had not been appreciated.

The blood sugar of the "Houssay dog" is notably labile. During fasting it may fall below 100 mg. per cent and after feeding may rise above 300 mg. The animal becomes a sensitive test object for either pituitary extract or insulin: the diabetogenic influence of the pituitary factor is enhanced in the absence of insulin and the hypoglycemic effect of insulin in the absence of the anterior pituitary secretion. It seems obvious now, therefore, that the clinical disorder, "hyperinsulinism," which Harris[60] ascribed merely to overactivity of the islands of Langerhans will have to be reconsidered; it may actually arise as well from anterior pituitary deficiency as from a disorder of the insulinogenic function.

Collip[30] who has reviewed the cogent literature is inclined to ascribe the relationship between the anterior hypophysis and diabetes to the secretion of two pituitary principles, one, "*blood-sugar raising*" (it might be designated, "B. S. R.") and the other, "*ketogenic.*" The B. S. R. principle is intimately associated with the somatotropic principle and may be identical with it; at any rate Collip's most highly purified "growth extract" has the property of increasing the blood sugar. This effect of the B. S. R. is obtainable in thyroidectomized animals. It is not found in the posterior lobe and is neither pitressin nor oxytocin. The B. S. R., according to the Houssay school, is soluble in water and in 60 per cent alcohol; it is insoluble in absolute alcohol, ether, acetone, benzene and chloroform. It is thermolabile and does not pass through ultrafilters. It is readily adsorbable on kaolin, by virtue of which property it is easily recoverable from normal human urine. Large quantities can be obtained from diabetic urine. When injected parenterally, it raises the blood sugar only after a considerable latency, but if it is introduced into the cerebrospinal fluid, the reaction is very prompt. Lucke[87] believes, therefore, that its action is primarily upon the central nervous system—perhaps upon a hypothalamic center.

From alkaline extracts of anterior pituitary substance is derivable a fraction that has a marked influence upon fat metabolism. Under its influence the ketone bodies in the blood are substantially increased. It has been designated the "Fettstoffwechselhormon" or "orophysin" by Continental investigators but in the American literature it is usually called the *ketogenic factor.* Unlike the B. S. R. it is closely associated with the thyreotropic factor, but it is effective in thyroidectomized rats (Funk[48]). According to Magistris,[94] the ketogenic factor can be obtained from pituitary glands that have been stored in acetone. The powdered gland substance is extracted with wa-

ter. It is ultrafilterable and dialyzable. It is insoluble in absolute alcohol, ether or chloroform, but is soluble in dilute alcohol and water. Again, unlike the B. S. R. fraction, it is not adsorbable by kaolin though it is by silica gel. It may be obtained from the euglobulin fraction of blood serum or, according to Funk,[46] by shaking human urine with benzoic acid and purification of the precipitate thus formed. The ketogenic principle is reported to increase the specific dynamic action of protein.

In clinical diabetes mellitus, both the carbohydrate metabolism and the fat metabolism are profoundly disturbed. The trend of recent endocrine research is to indicate that the two aspects of the disease are intimately bound up with the B. S. R. and the ketogenic influences of the anterior lobe of the pituitary gland. It seems probable that the "diabetogenic principle" which is frequently alluded to in present-day literature actually represents a composite of these two factors.

Emphasis is due upon the fact that the foregoing discussion of pituitary physiology amounts to no more than an outline sketch which may serve as a skeleton for the organization of the complex mass of details with which anyone reading further into the subject will be confronted. Whether all the functions that are now ascribable to the pituitary represent the operation of separate individual hormones is doubtful. The possibility of mere mathematical permutations should be kept in mind. It is theoretically possible to derive from four factors sixteen characteristic combinations. Thus no more than four or five hormone entities need necessarily be postulated to account for the multiplex influences that the pituitary gland has been shown to mediate. Too, there is the possibility that the gland may secrete only a small number of mother substances from which the reacting tissues may derive this or that final active product in accordance with local needs or conditions. In any case the mere derivation of characteristic active bodies from glandular substance by no means assures their hormone status; they may be merely chemical artifacts.

Despite the assiduity with which researches on pituitary physiology have been prosecuted much that is fundamental remains yet to be discovered. The relationships that have been already disclosed are complex and stand in large measure in need of further resolution into their elements. In such studies it is important to realize that the conditions in the living tissues that determine the reactivity to a given hormone may be quite as important as the properties of the hormone itself. These reaction factors must be rigorously controlled if puzzling discrepancies of data are to be avoided. It now seems sufficiently evident that either directly or through their influence on the various endocrine glands and the nervous system the pituitary hormones have important regulatory influences upon most or all of the vital functions. A large problem, and one toward the solution of which only a beginning has been made, is the translation of pituitary physiology and pathology into terms of clinical symptomatology. For a further account of more recent developments in pituitary physiology Evans' review[41] may be consulted.

CHAPTER LXXIV

THE TESTIS

As has been recognized for centuries, the male sex glands are the primary source of the various qualities, physiological and psychological, that are connoted by the term, *virility*. Castration has been widely practiced both in human subjects and in farm animals, and the chief effects of that operation are matters of common knowledge. The testes, like the ovaries, have to be considered in their relationship both to sex and to reproduction.

Sex has been defined as "the sum of the peculiarities and functions that distinguish a male from a female organism." Some of these peculiarities have to do only indirectly with reproduction. The testis produces not only fertilizing elements, the spermatozoa, but also one or more hormones that have to do with the many physiological and psychological adaptations by which reproduction is brought about. In many of the lower forms of life reproduction is carried on by processes that are not sexual. The process of sexual reproduction is foreshadowed in that of conjugation in which the parent organisms fuse as a whole and subsequently divide to constitute the offspring. Early in the evolution of the higher forms the *gametogenic* tissues were set aside from the remainder of the body to be incorporated in the gonads.

Ordinarily there is a rather sharp demarcation between males and females but both testes and ovaries may occur in the same individual; in some species males and females are scarcely distinguishable. In the case of certain animals, for example the fowl, the same individual may successively possess the gonad tissue and the functions of the female and the male. In the human species true *hermaphroditism* sometimes occurs and normally each sex has in rudimentary form the reproductive structures and impulses of the other. In addition to the reproductive organs, proper, there are a variety of *secondary sexual characteristics* such as the horns of the stag, the mane of the lion, and color among birds. The distribution of hair in man is a typical example of a secondary sexual characteristic.

The segregation of the sex cells in different individuals has necessitated a variety of mechanisms and reactions for bringing the germinal elements together. The structure of the respective reproductive organs is an obvious case in point. The prostate of the male appears to have the primary function of protecting the viability of the spermatozoa and the seminal vesicles share in this function as well as to add bulk to the ejaculate. The utility of accessory structures of the female that secrete lubricating fluids is clear. The same is true of the orgastic reflexes of the male. The function of the female orgasm is not certainly established but a plausible surmise is that it serves to aspirate the ejaculate. Also, it may stimulate ovulation.

In addition to the anatomical and physiological differences between males and females there have arisen also distinctive sexual instincts. These control the behavior of the individuals in their reciprocal relationships, such as courting or estrus and mating, and they initiate such activities as nest building and

feeding of the young. In many animals the sexual instincts are operative only during the breeding season. Various secondary sex characteristics are exaggerated during the breeding season and wane with its passing. In the higher forms such periodical changes in the secondary sex characteristics are directly under the control of the gonads.

In most mammals the testes emerge from their initial intra-abdominal position into an extension of the body cavity, the scrotal sac. Occasionally, in man, they are retained within the body cavity to give rise to the condition known as *cryptorchidism*. The sex cells in the cryptorchid testis remain at an infantile stage of development, hence the subjects are always sterile. They often possess, however, their full complement of virile instincts and normal secondary sex characters. This fact establishes the high probability that at least the chief hormone function of the testis is mediated, not by the gametogenic tissue but by the interstitial cells of Leydig, which can develop in an approximately normal way even though the testis fails to migrate. The chief factor that prevents the development of the gametogenic tissue in the cryptorchid testis seems to be the relatively high temperature to which it is subjected. Sand[121] and others have shown that males can be easily sterilized by subjecting the gonads to elevated temperature of a degree otherwise harmless. In some animals, for example the rat, optimal temperature conditions are maintained by extruding or withdrawing the testes through the patent inguinal canal.

While there is no question that the changes characteristic of puberty are dependent upon gonad factors, there is some question as to the part played by the testes in the earlier years. Despite the fact that males and females are characterized from time of fertilization by a difference in the chromosome complex of the somatic cells the human infant is largely neutral both somatically and instinctually. As growth proceeds, however, a certain amount of differentiation occurs in the bodily form and perhaps in the disposition, though the latter may be due largely or entirely to social conditioning. With the onset of puberty the dimorphism becomes marked. That the gonads may have a significant influence even during intra-uterine life is suggested by the occurrence of *free-martins* in cattle. A cow may give birth to twin calves of opposite sex, each of which is normal. But occasionally the placentas to which the twins are attached become fused so that the blood streams of the two intermingle. In such cases the female shows considerable transformation toward the masculine form and remains sterile throughout life. This effect is plausibly to be ascribed to a masculinizing influence derived from the testes of the brother.

Castration of domesticated animals is a widely practiced farm procedure. The results of the operation are evident in the contrast between the docile ox and the aggressive bull. When the operation is practiced at the prepuberal stage the results are quite similar in all the higher animals. The subjects continue to grow to, or beyond, adult proportions but fail entirely to undergo the psychic changes of normal puberty. The resulting state represents essentially a persistence of a neutral asexual form rather than a transformation to the feminine form as popularly supposed. In some forms the rate of growth is somewhat retarded, but this may be masked by a tendency to lay on fat. The arresting of proliferation in the growth zones of the long bones fails to take place as in normal animals in the late puberal stage, hence the final stature is

likely to be greater than normal. Following castration the penis, prostate, and seminal vesicles cease to grow or, if the operation is delayed until the growth has taken place, a regression occurs. Relatively few influences on the metabolic processes have been detected though there is often seen a slight but sensible decrease of the oxygen consumption rate. This, however, may mirror relaxation of the subject rather than a depression of the true basal rate. Steinach[134] has recently reported that following castration the urinary creatine output is increased.

Aside from changes in the instinctual drives and emotional reactions no significant influence on the functions of the central nervous system has been noted but Wheelon[141] reported rather marked decrease in the irritability of the sympathetic nervous system of castrated dogs, an effect that was largely corrected by subsequent testicular grafts. The spontaneous activity of rats as measured in automatically recording exercising cages is markedly decreased by the operation.[68]

The relationship between the testes and psychosexual behavior is close. The common fowl is a favorable subject for experimentation directed to this problem. When the primary gonads are removed from either young males or females the result is an overgrown creature, the capon or the poulard, as the case may be. The erstwhile male remains timid, does not develop the masculine spurs or comb, and never crows. He shows no evidence of erotic interest in females. Particularly instructive is the fact that the poulard may subsequently regenerate functional gonadal tissue and this may be either testicular or ovarian. The bodily and dispositional changes appropriate to either sex then appear in accordance with the type of gonad regenerated. It thus appears that not only the quantity but also the quality of the gonadal hormonal influences are determined by the nature of the primary sex organs. This is a point of considerable significance in clinical psychopathology.

In the human species after early castration, the proliferative activity in the epiphyses of the long bones may continue well into the third decade whereas elongation of the trunk fails to take place in equal degree. Thus there develops a characteristic configuration, the arms and legs, hence the span and height, being quite out of proportion to the trunk length. The abnormal appearance is accentuated often by lean, long hands and fingers, toes and feet. The larynx remains small and of the infantile type, hence the voice remains high-pitched. The skin is delicate, pale, sallow, and liable to premature wrinkling which gives the subjects an appearance of early senility. The subjects are likely to be obese but even in the less common thin type the fat is peculiarly distributed. The sites of election are the buttocks, trochanters, breasts, lower abdomen, pubic region and lateral sides of the upper eyelids. The facial and body hair is scanty in amount and the pubic hair assumes the feminine pattern.

When castration is performed in the earlier years all genital development promptly ceases and potentia is never gained. When it is carried out after the sex functions are well established, a varying degree of sexual activity may persist. The effects of the operation on temperament in man have been much debated. Commonly the eunuch is reported as lacking in initiative and stamina. The mentality as such is apparently not affected. The instinctual drives are, of course, materially influenced, with all erotic propensities eradicated. Through the operation of disease and, particularly, as a result of

deficiency of the anterior pituitary, a condition of partial gonadal deficiency may arise. The effects approach those of castration, depending in part upon the time of onset of the disorder and in part on its severity. Two factors render a clean-cut appraisal of the effects of castration in man somewhat difficult. The stigma attached to the condition tends to make the individual self-conscious and to feel inferior. These factors may produce a profound effect upon the disposition quite aside from the hormonal influences. The second difficulty is that if the sex functions have become well established before the operation there is considerable tendency for them to persist. This topic has been discussed at further length in another publication.[70] The clinical aspects of gonadal deficiency in man are discussed at greater length by Lisser.[83]

Many attempts have been made to ameliorate the effects of definite or assumed testicular deficiency by the use of *grafts* or *gland extracts*. Indeed, the first formal experimental approach to endocrinology seems to have been made by Berthold when in 1849 he discovered the efficacy of bits of testicular tissue introduced into the peritoneal cavity in preventing the onset of the capon characteristics following castration in the fowl. The problem was taken up again in a systematic way by Steinach[133] early in the twentieth century. He removed the ovaries from female guinea pigs and replaced them with the sex glands of their twin brothers. These artificial males thereupon outgrew their female controls and showed the skeletal characteristics, the coarser hair growth and the pugnacity of normal males. The reverse experiment of feminizing castrated males by ovarian grafts was also successful. Steinach's work has since been confirmed by various other investigators, including Lipschütz,[82] who has reviewed the literature at some length.

The extent to which testicular grafts may be effective in the restoration of the waning bodily and sexual functions of old age is problematic. That many elderly men have testified to beneficial effects is unquestioned but to what extent results may have depended upon suggestion rather than hormonal influences is uncertain. In occasional cases, such as that of Lisser,[83] objective evidence of effectiveness has been obtained. In this instance a testis removed from a vigorous young man was transplanted into a man fifty years of age. The recipient had always been beardless; his voice was high-pitched, and it was stated that he had had no experience of sexual desire or activity. Within three months an awakening of sexual activity was reported. Objectively, the development of a beard and increased body-hair growth were noted.

The case for *testicular extracts* has until recently been little better than that for gland grafting. In 1889 Brown-Séquard,[25] then an elderly man, reported that injection of glycerin extracts of fresh testis into himself had had a remarkable effect in restoring his waning vigor. The experiment, however, has often failed of confirmation in the hands of other investigators and the chief significance of his report was the widespread interest that was aroused thereby in the subject of the internal secretions. Numerous attempts have been made by the use of testicular extracts of different sorts to overcome the effects of castration in experimental animals. While some successes have been reported many negative results have been secured. The literature is reviewed by Lipschütz.[82]

In the light of more recent work it would appear that the chief difficulty in the preparation of active testicular extracts has been the minute quantity in which the active principle occurs in the gonad tissue. The first successful

extraction of an active principle from testicular substance was reported by McGee.[92] The work was done in the laboratories of Moore and Koch who, with their collaborators, have reported numerous subsequent studies. The potency of the active testis extract can be demonstrated in a number of ways. The most practicable is to inject it into capons in which it causes striking growth of the comb, wattles, and other male head adornments. The response can be detected in one to three days, and regression of the comb promptly takes place when the extract is withheld. Funk and Harrow[47] succeeded in obtaining a similar active substance from the urine of men. They reported that it is absent from the urine of boys and of the aged. Similar success in the isolation of active material from urine was reported in 1931 by Butenandt[27] who succeeded in isolating it as a crystalline body and determining its composition. He gave it the name *androsterone* and assigned to it the formula, $C_{19}H_{30}O_2$. The same substance has been synthesized by Ruzicka and its composition confirmed. Study of this material soon indicated that it differed somewhat from the active principle of testicular extracts, and notably in its smaller activity per capon unit on the seminal vesicles of castrated rats. It appeared, therefore, that androsterone is not the chief principle of testicular extracts. David in 1935 succeeded in obtaining from testicular substance a crystalline body, which was of the sterol type, having high activity on both capons and rats. This he has named *testosterone*. It has the composition, $C_{19}H_{28}O_2$. Several other compounds chemically similar to these two have recently been prepared. It is proposed that all such substances having physiological potency be called *androgens*.[104] Deanesly and Parkes[35] have recently reviewed the literature on the androgens and have reported studies of their chemistry and relative potency. In general, the androgens all have the properties of causing comb growth in capons and preserving the seminal vesicles and prostate of mammals from the atrophic changes that normally follow castration.

From the fact that it occurs in testicular substance it may be surmised that testosterone represents a true hormone and androsterone a urinary excretion product. That the true testicular hormone is a compound of this type can scarcely be doubted, but in what precise form it is thrown from the glands into the blood stream has not and, from the types of study that have so far been made, probably cannot be determined. Both testosterone and androsterone are of high physiological potency. For example, 3 mg. daily of androsterone suffices to maintain normal seminal vesicle growth in mature rats. There is evidence that larger doses have a depressive effect upon the anterior pituitary, and that this in turn causes depressive effects in the testes of the intact animal. The therapeutic value of the androgens has not yet been adequately determined but they are effective in true hypogonadism.

That the testis has a true hormone function is further indicated in the rare cases in which neoplasms of those organs produce *sexual precocity* in the subjects. The classic case of Sacchi[119] is typical. Beginning at the age of five years the subject began to grow at a rapid rate and to develop the secondary sexual characteristics. At nine years of age he was 143 cm. tall with well-marked hair growth on face, extremities, and pubis, and the genitalia were approximately of adult size. During this period a carcinoma of the left testis underwent considerable enlargement. The affected organ was removed, whereupon the signs of sexual precocity rapidly receded. A few months later the beard

and hair on the extremities fell out, the penis became smaller, erections and ejaculations ceased, and the voice, which had reached low adult pitch, again became childish.

Numerous other instances of sexual precocity in boys have been reported but these, in general, have their primary origin in other endocrine organs—the adrenal cortex, the pineal, or the anterior pituitary. Commonly such cases are marked by excessive development of the genital organs, early deepening of the voice, and excessive body growth. Premature appearance of both the temporary and the permanent teeth is common. Genuine sexual activity, including the production of spermatozoa, has been reported even within the first year of life. The growth of the skeleton is at first stimulated but commonly the testicular hormone intervenes within a few years to stop the proliferative activity in the epiphyseal zones of the long bones, hence the ultimate stature is usually no greater than that of the normal adult and it frequently is materially less. The progress of skeletal maturing can readily be followed by x-ray studies of the wrist. Indeed, the progress of carpal ossification may serve as a "physiological time clock," to indicate the relative degree of physiological maturity in general (Todd).

The occurrence of *hypergenitalism* in the prepuberal years is unquestioned. Whether a comparable condition occurs in adulthood is curiously uncertain. There is a condition known clinically as *satyriasis* in which, as the name implies, eroticism goes to inordinate lengths. Whether this is due, however, to endocrine factors, to abnormality of the nervous system, or to social conditioning has not been satisfactorily determined. The fact that the testes are subject to depression of hormonal functioning during adulthood suggests, however, that hyperfunctioning also might occur. Fancher[42] has recently reported what purports to be the first case in the literature of authentic hypergenitalism in a man.

The evidence is now substantial that the testis under some conditions may exert a depressive hormonal influence upon the anterior pituitary. McCullagh[87] has reported the preparation of an extract believed to derive its potency from gametogenic tissue that has as its outstanding effect such a depressive influence. He proposes for it the name, *inhibin*. The work as yet lacks confirmation.

CHAPTER LXXV

THE OVARY

In addition to the production of ova, the female gonad also has important endocrine functions. At what stage the ovary begins to secrete hormone is not clear. That it initiates such secretion even before birth has been affirmed but positive evidence that this is true is largely lacking. Frank[44] by actual extraction methods was unable to detect any significant concentration of hormone in the prenatal ovary. Similarly scanty is the evidence regarding ovarian endocrinology during childhood. The young girl is largely neutral, sexually, but even during childhood some degree of feminine differentiation is manifested—particularly in the form of the pelvis. In view of the fact, however, that the two sexes differ in chromosomal constitution, such structural dissimilarities do not necessarily indicate the operation of hormone control. But with the onset of puberty the fundamental intervention of ovarian humoral factors becomes clear.

Ovarian Deficiency.—Gonadectomy is performed much less frequently in females than in males, but it is clear from animal experimentation that the operation in the prepuberal years causes a very similar persistence of neutral body form and lack of development of definitive reproductive instincts in either sex. The precise results of ovariectomy in the human species have been little studied, but in a few instances it has been noted that girls subjected to this operation become abnormally tall and fail to achieve development of the breasts; the axillary and pubic hair likewise fail to appear.

Through developmental anomalies, however, and particularly deficiency in anterior pituitary secretion, a condition more or less closely approaching that due to ovariectomy arises. The condition is often referred to as *female eunuchoidism* though the term is a misnomer; a preferable term is *sexual infantilism*. The condition is marked by a lag in the appearance of the puberal transformations and a halting of them short of completeness. Underdevelopment of the breasts, scantiness of pubic and axillary hair and persistence of the juvenile type of uterus and vulvar structures are the chief morphological indicators of the condition. Menstruation may be entirely absent or may be late in appearance and scanty in amount. The primary sex impulse and the secondary reproductive instincts are depressed.

In contrast with the paucity of data regarding the results of gonad deficiency in girls there is abundant evidence as to the effects of that condition in women. Following surgical removal of the ovaries at any age during the reproductive epoch the condition known as artificial *menopause* arises. Menstruation ceases; the uterus and breasts undergo regression. The subjects often increase in weight with an accumulation of adipose tissue especially in the region of the hips. A tendency toward masculine hirsutism not infrequently arises. The sympathetic nervous system goes through a stage of abnormal reactivity which leads, among other things, to periodic vasomotor changes in the skin. Subjectively these are experienced as "hot flashes." They can easily be induced by the administration of adrenalin, and it is not unlikely that

they are brought about or at least accentuated at times by episodic discharges from the adrenal medulla. That the central nervous system shares in the increased reactivity is indicated by emotional lability and often by a persistent sense of inner tension. In ovariectomized animals, the primary sex impulses are largely or entirely obliterated, but women who have undergone the operation report considerable degrees of variability in this respect.

In gynecological practice the occurrence of various manifestations which may plausibly be ascribed to functional ovarian deficiency is frequently noted in women who had previously attained normal development. These may or may not be associated with sclerotic or other regressive changes in the ovaries. Typically, the picture in the individual case is somewhat variable, a fact which suggests that the production of ovarian hormone may likewise vary from time to time. From the fact that ovarian deficiency as seen in childhood or in the postclimacteric period is a benign condition it seems probable that the symptoms of so-called *functional hypogonadism* in women are due rather more to imbalance of hormones than to pure deficiency.

Complete destruction of the ovaries deprives a woman not only of such hormones as may arise in the follicles and the interstitial tissue but of those in the corpus luteum as well. The differential effects may be studied by excision of the corpora lutea, leaving the other structures intact. This operation results in a disturbance of the functions having to do with pregnancy. If the operation is performed before or soon after fertilization, the uterus quickly loses its ability to fix the ovum, which passes through and is aborted. If the operation is deferred until *nidation* is under way, the embryo soon loses its functional relationship with the uterus and is aborted. While in some animals the presence of the corpus luteum is necessary throughout a considerable proportion of the pregnancy in order to forestall abortion, in women it becomes dispensable within the first month. A plausible suggestion is that the function of continuing the pregnancy is early taken over by placental hormones. This suggestion agrees with the fact that the placenta in the higher primates is a strikingly more prominent structure than in other animals.

Fraenkel (1901; 1903; 1910) was the first to provide experimental proof that the nidation and nutrition of the embryo depends on the corpus luteum. He showed that when the corpora lutea were removed from both ovaries of pregnant rabbits before implantation or at any time up to the eighteenth day, the pregnancy was terminated. From this it became apparent that the corpus luteum is necessary for the implantation of the ovum and for the maintenance of the proper uterine condition for the development of the embryo. It appears, however, that the necessity of the corpus luteum for the latter function varies in different species. In the guinea pig, for example, removal of the corpora lutea after the second day following coitus may not interrupt the pregnancy; this stands in contrast to the results obtained in the rabbit. It was shown by Leo Loeb that if any foreign body, such as a glass bead, is placed in the uterus at the time a corpus luteum is developing, a definite mass of decidual tissue is produced at the point of contact. Mere scratching of the mucosa has a similar effect. Deciduomata of this nature will not form if the corpora lutea are first destroyed. It would appear, therefore, that the ovum acts as a stimulus to a uterine mucosa which must be maintained in a certain state of nutrition and sensitization by the corpus luteum.

Ovarian Hormones.—The lines of evidence bearing on ovarian functions that have been derived from extirpational experiments have been supplemented in various important ways by studies of the influences of a variety of ovarian extracts and active principles. Some of these presumably represent veritable ovarian hormones though logically adequate proof that this is the case is not available in any single instance. Although previous investigators had made claims of having secured potent ovarian extracts, it was not until 1923, when Allen and Doisy[7] reported their results from the use of follicular fluid, that satisfactorily consistent evidence began to accumulate. These investigators showed that either the raw fluid itself or suitably prepared extracts from it have a marked influence in restoring the sexual functions and structures of spayed rats. From the fact that the animal is again brought into estrus, the active principle found in the follicular fluid has been designated as *estrogenic*.

Fig. 363.—Effect of injection of follicular extract into eight-week-old rabbits. Animals were litter sisters. No. 807 received 2 mg.; No. 805, not injected, was killed at the same time as No. 807 for control. No. 806 received 1 mg. daily for four days and No. 809 1 mg. daily for eight days. No. 808, uninjected control, killed on same day as No. 809. (After Doisy, Ralls, Allen and Johnston.)

As a matter of fact a considerable number of preparations have estrogenic properties. The literature on this subject has become extensive and many technical details regarding such substances are now available, but the interrelationships and the physiological significance of the several estrogenic materials have not as yet become clearly known. Animal sources of estrogenic material other than the ovary itself are the urine of nonpregnant women; the blood, urine and amniotic fluid of pregnant women; the human placenta; the urine of pregnant mares and of stallions; and the urine of men with testicular neoplasms, especially teratomata. Similar materials have also been derived from plant sources. Not only may the estrous reactions be induced directly by these various substances, but they may be secondarily set up by hormones from the anterior pituitary, the placenta and perhaps other endocrine glands which stimulate the ovaries.

In addition to arousing the mating impulse of the female animal the estrogenic hormones have the property of inducing rapid growth in the accessory genital organs (Fig. 363). Changes in the vaginal wall are especially characteristic, a fact that has led to the widespread use of vaginal changes in rodents for the assay of estrogenic materials. These changes can readily be detected by examination of the vaginal fluid. Other effects that can be elicitable are changes in the plumage of certain birds, reddening and swelling of the sexual skin of various higher primates, growth of the mammary glands and proliferation of the endometrial wall. The latter change is accompanied by vasodilatation of the capillaries. The muscular activity of the uterus and the fallopian tubes appears also to be controlled by estrogenic hormone. Coincident with the oestrual increase of the sex urge there is also an augmentation of spontaneous bodily activity.

The threshold of reactivity to estrogenic substances varies in different structures. In rats and mice more is required to bring about endometrial proliferation than changes in the vagina and to elicit the mating reactions requires a still greater amount.

The appearance of estrogenic material in the urine of women varies in relation to the menstrual cycle; the curve of hormone concentration shows two peaks, the first and smaller occurring about the mid-menstrual period and the second in the early part of the last week preceding menstruation. The first peak is apparently correlated with the maximal growth of the follicle and the second with the height of corpus luteum activity. During pregnancy there is a gradual rise in the excretion of estrogenic substances. The output becomes clearly apparent in the latter half of the second month and continues throughout the period of gestation. After parturition the level of excretion falls rapidly to reach the normal value within four or five days. Further details of the physiology and pharmacology of the estrogenic principles are available in a review by Allen[6] in which are cited several important monographs.

A considerable number of potent estrogenic materials under a variety of names are available commercially (Biskind[18]). The activity of these is due in whole or in part to certain active principles now available in crystalline form. The first to be obtained was *theelin,* $C_{18}H_{22}O_2$. This is designated also as *ketohydroxyestrin,* or *oestrone.* Somewhat less active when administered by subcutaneous or intramuscular injection but more potent when taken by mouth is the trihydroxy compound *theelol* or *oestriol,* $C_{18}H_{24}O_3$. For further information on the somewhat complex chemistry of the estrogenic principles recent monographs should be consulted.[6, 10, 57]

The estrogenic hormones are used therapeutically in a variety of conditions authentically or presumably due to deficiency of the ovarian secretions. They have proved to be most valuable in correcting certain menstrual abnormalities and amelioration of the subjective symptoms of the menopause—naturally or surgically induced. Numerous instances of successful results in the treatment of psychoneurotic symptoms other than menopausal have also been reported but an evaluation of the effects of the preparations, as distinct from the effects of suggestion, is difficult. Commonly, women are reported to recognize no influence of estrogenic preparations on the primary sex urge, but in occasional instances such effect is reported to be rather marked.

The relationship of the corpus luteum to pregnancy as indicated by the results of extirpation experiments has been largely confirmed by a study of effects of chemical derivatives of corpus luteum tissue. As a generic term for the active principles in such extracts the name *progestin* has been suggested.[103] One progestin has been obtained in crystalline form, and this is properly referred to as *progesterone*. This is a diketone having the formula, $C_{21}H_{30}O_2$. The synonym, *luteosterone,* is frequently used in the European literature. Progesterone exists in an alpha-form melting at 128° C., and a beta-form melting at 121°. The physiological significance of this difference is not known. Chemically, progesterone is closely related to the estrogenic principles as well as to the male hormone, androsterone; it is structurally similar also to certain cyclic compounds having carcinogenic properties.

Progesterone is not potent when given by mouth, either because of failure of absorption or because of inability to withstand the digestive enzymes; it is commonly administered intramuscularly in oil. It is assayed in terms of its ability to produce in castrated rabbits the uterine changes characteristic of pregnancy. The induction of progestational changes in the uterus can be obtained only if the uterus has first been "primed" by estrin. Progesterone has the property of preventing abortion following extirpation of the corpus luteum and permitting the pregnancy to run to full term. In some forms, notably the guinea pig, it demonstrably serves as a stimulus for the production of the maternal part of the placenta. Different observers have succeeded in producing with progestin the premenstrual type of endometrium in monkeys. In ovariectomized women after preliminary treatment with estrogenic substance progestin is able to bring about the further normal premenstrual changes. Progestin has an inhibitory effect upon the uterine musculature; the favorable influence of the material that has been reported clinically in forestalling threatened abortion may be correlated with this property. The part that progestin plays in the menstrual phenomena will be discussed in a subsequent section.

Whether the ovaries ever secrete estrogenic hormone in sufficiently excessive degree in adults to give rise to significant clinical effects is uncertain. The condition of *nymphomania* with its excessive sexual urge might plausibly be ascribed to such a cause, but the element of abnormality of the nervous system is difficult to exclude. A considerable number of well authenticated cases of precocious puberty in girls have been reported and this for the age in which it occurs amounts, of course, to *hypergonadism*. While the condition is more commonly due primarily to disturbances in other endocrine glands it may have its primary origin in the ovaries themselves. In veterinary practice abnormal persistence of the corpus luteum, usually in cystic form, is a well recognized cause of sterility. This is brought about by the halting of the sex cycle at the phase which is dominated by progestin. There is some clinical reason to suppose that a similar situation in women may give rise to sterility.

In the foregoing discussion considerable simplification has been made. The action of the ovarian hormones as well as their production is in considerable measure determined by conditions in related organs. Some of the complicated relationships that are involved will be discussed in the next chapter.

CHAPTER LXXVI

ENDOCRINE FACTORS IN REPRODUCTION

That the reproductive activities are under endocrine control has been indicated in various preceding paragraphs. The relationships involved are notably complex and may be further discussed from the standpoint of the various reproductive functions, themselves.

It is probable that normal *sexual development* cannot occur in the serious deficiency of any of the important hormones. In some cases these seem to be important primarily if not solely in their function of assuring a sufficient degree of metabolic and nutritional normality to support the biological processes involved in sexual development. In other instances the relationships appear to be specific.

One of the striking results of *thyroid deficiency* is a general retardation of development in which the sex organs and reproductive instincts share. The gonads themselves and the accessory reproductive structures remain small or, in lesser degrees of thyroid deficiency, show a lag in development. In women in whom menstruation has become well established high degrees of intervening thyroid deficiency may lead to depression of the function but with lesser degrees profuse and abnormally frequent flow is more likely to be seen. In such cases thyroid medication often corrects the menstrual abnormality. In males who have achieved sexual normality the intervention of thyroid deficiency leads to decreased libido and various degrees of impotency. In both sexes sterility that is subject to amelioration by thyroid medication may arise.[99]

The sexual precocity following the use of *thymus extracts* as reported by Rowntree[117] may be indicative of a specific hormonal control of reproduction but various investigators have failed to confirm the findings.

Whether the *parathyroid glands* have any important relationships with reproductive activities is not evident.

In the case of the male the reproductive activities are relatively simple and the known hormonal factors involved in their control have been previously indicated. The relationship between the testis and the *pituitary* is particularly close. In the case of early anterior lobe deficiency normal development of the gonads cannot take place; if such development has been achieved prior to the onset of the pituitary deficiency, functional activity cannot be maintained. A partial exception to the foregoing statement is that in certain instances the secretion of gonadotropic hormone may persist when the production of somatotropic hormone is deficient, i.e., pituitary dwarfs are occasionally fertile. Experiments on parabiotic rats have afforded evidence that castration removes a check on the anterior pituitary and so leads to an increase in its production of gonadotropic material. Also, implants of anterior pituitaries from castrated animals show greater than normal gonadotropic potency. The theory has been advanced that the activities of the two glands are kept adaptively in balance; the rate of production of testicular hormone serves to determine that of the con-

trolling pituitary secretion and vice versa. Antecedent changes in the anterior pituitary probably play an important rôle in determining the seasonal periodicity of the reproductive activities of many animals.

The hormonal relationships involved in the reproductive activities of women are more complex than is the case in men. As previously mentioned, there is some probability that ovarian hormones determine in some measure the bodily form of the girl as contrasted with that of the boy, but it is not until the onset of puberty that hormone intervention becomes clearly evident. The bodily and psychological changes of puberty take place only as adequate supplies of primary gonadal hormones are available. The secretion of these hormones is in turn dependent upon the gonadotropic hormones of the anterior pituitary. Throughout childhood the ovaries in periodic succession continue to produce maturing graafian follicles, but these fail to dehisce; they undergo regressive

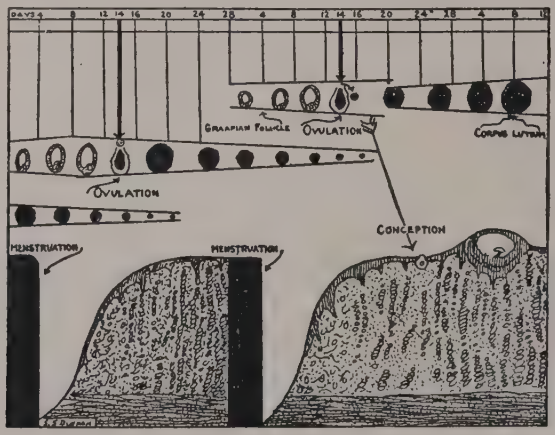


Fig. 364.—Diagram showing the relationship between the ovary and the uterine changes of menstruation and pregnancy. The lower part of the diagram represents the endometrium with its contained glands. Note the nidation of the early embryo and, further to the right, the attached embryo and beginning placenta formation. Courtesy of Dr. Benjamin Parvey. Published in Endocrinology, 16: 225, 1932. (From Hoskins: The Tides of Life, New York, 1933, W. W. Norton and Company.)

changes and their contents are absorbed. At about the twelfth year, in temperate climates, and a few months earlier, in the warmer countries, one of the follicles ruptures at the surface of the gonad, liberating an ovum. Fertilization now for the first time is possible and the transition point from puberty to adulthood has been passed. This transition is objectively signalled by the onset of menstruation.

Menstruation.—The menstrual cycle may conveniently be divided into four periods: the resting stage, the interval stage, the premenstrual stage, and the destructive stage.

The *resting stage* comprises the four or five days immediately following the cessation of the preceding flow. During the flow the lining tissues of the uterus are to a considerable extent broken down and discharged. Consequently at the beginning of the resting stage the mucosa is very thin. The uterine glands are

relatively sparse, narrow and straight. At this stage the ovary contains a corpus luteum formed in the previous cycle, but its secretory function is now on the wane. It is diminishing in size and losing its characteristic yellow color to become a little later the corpus albicans, a structure that so far as is known has no active function. During the resting stage a new graafian follicle is progressing toward dehiscence and forming follicular fluid with its contained hormone—presumably theelin. The best evidence indicates that the production of theelin at this stage is shared by the surviving corpus luteum.

The *interval stage* of the cycle lasts about ten days. It is a period characterized by adaptive changes in the uterus preparatory to the reception of the next ovum that may be discharged. The endometrium rapidly thickens and the uterine glands lengthen and permeate more widely through the endometrium; the blood supply increases to a marked degree. Coincident with the growth of the endometrium, activities in the ovary continue. Within the first half of the interval stage the follicle ruptures. Thus ovulation occurs about midway between the menstrual periods. At this time the production of theelin is at its height. Immediately after discharge of the ovum, rapid multiplication of the cells lining the follicle ensues to give rise to a new corpus luteum. The newly formed lutein cells begin, presumably at once, to form progestin, whose influence on the uterus is now added to that of the theelin. The weight of available evidence indicates, however, that the corpus luteum at this stage participates also in the formation of theelin. The newly discharged ovum enters the fallopian tube through which it is swept along toward the uterus. It is now ready for fertilization, and if a spermatozoon is available the two gametes fuse to give origin to the embryo. Although clean-cut data on the point have been difficult to secure, considerable evidence is now available that, at this period when the production of ovarian hormones is at its height, the woman experiences an accentuation of sexual desire. In the subprimate forms it is at this point in the ovarian cycle that the phenomena of *estrus* occur. Commonly in these forms it is only at this time that the male is accepted.

Succeeding the interval stage is the *premenstrual stage,* ten days in duration. Under the further influence of the ovarian hormones the preparatory processes in the endometrium continue. The uterine glands increase in diameter and in length and assume the characteristic corkscrew form. They become distended with secretion. The relative parts played by the estrogenic and luteal hormones at this period are somewhat uncertain, but probably the latter assumes the dominant rôle. In the latter part of the premenstrual stage the endometrium has reached its maximum degree of preparedness for the prospective pregnancy. If fertilization occurs, the corpus luteum continues to secrete at a maximal rate and brings about the changes characteristic of pregnancy. On the other hand, should fertilization not occur, the hormonal activities of the ovary and corpus luteum rapidly wane and the endometrium, deprived of their stimulating influence, begins to regress. This point marks the onset of the destructive stage when the menstrual flow begins. From the congested capillaries of the endometrium diapedesis occurs. The parts of the endometrium nearest the lumen of the uterus begin to break down and with their disintegration the capillaries rupture and the menstrual flow becomes fully established. During the four days that normally comprise this period, the dismantling

processes in the endometrium are completed, the detritus is all discharged, the ruptured blood vessels are closed and the succeeding cycle begins.

The processes just described comprise the common type of menstruation. In monkeys, however, another type, anovular menstruation, has been demonstrated to be of rather frequent occurrence and accumulating evidence indicates that this type also occasionally occurs in women. Presumably the earlier hormonal activities are approximately the same in both types, but in the anovular the ovum is retained within the follicle which thereupon becomes atretic without the formation of a corpus luteum.

The foregoing sequence of events serves to fix the period of fertility in women. From observations made in the course of laparotomies and, more recently, by direct study of the time of apearance of ova in the fallopian tubes, the time of ovulation has been rather definitely fixed. Allen and Pratt[8] have developed a technique of washing out the tubes exposed at operation. They have not been able to recover ova earlier than the twelfth day nor later than the sixteenth day after the beginning of the preceding menstrual flow. The appearance of the ova themselves, as well as signs of recent rupture of ovarian follicles, served to complete the evidence. The time of ovulation, therefore, occurs at the midmenstrual period, and fertilization is possible only during the brief period that the ovum is in the fallopian tube or uterus from which, unless it is fertilized, it is soon discharged.

The most uncertain feature in determining whether a given coitus may be fruitful is the possible length of survival of male gametes within the genital tract of the female. The earlier belief was that spermatozoa might persist in a state of functional efficiency for as long as ten days after coitus, but the more recent and more reliable evidence indicates that the period is much shorter.[6] In the case of women, therefore, who enjoy regular menstrual cycles the "safe period" may be relatively accurately fixed. Considerable irregularity, however, is not uncommon, and the possibility is perhaps not wholly excluded that the act of coitus, itself, may lead to precocious ovulation. In the rabbit, indeed, ovulation takes place only after coitus, the immediate stimulus being a discharge of anterior pituitary gonadotropic hormone brought about as a nervous response to that act.[22]

Many women report a sense of well-being and efficiency during the midmenstrual period at the time when the hormone output from the ovary is at its maximum level. At this time, too, the oxygen consumption rate is at its high point for the given cycle. It then falls off to reach its minimal level at the time of the flow. During uterine bleeding, when hormone production is at the lowest level, many women experience a sense of tension and irritability. This may be accentuated by dysmenorrhea but it seems to occur even when local pelvic pain is absent. It is known from animal experimentation that deficiency of ovarian hormone causes an augmentation of sympathetic irritability and the brain seems to share in this characteristic.

That the periodicity of the menstrual phenomena depends upon variations in the rate of secretion of ovarian hormones is clear. The cause of the periodicity in these secretions resides largely in the anterior pituitary. As previously pointed out, this structure and the ovary stand in functional relationship whereby an ebb in the ovarian hormone tide serves to bring about augmented secre-

tion of gonadotropic hormone. This causes increased ovarian activity which in turn brings about a depression in the anterior pituitary. The lag in these reciprocal responses gives time for successive waves of activity; without this lag, the two structures would presumably come into equilibrium and the periodicity disappear. There are suggestions in the recent literature that the relations of the corpus luteum and of the ovary, proper, with the anterior pituitary are more or less independent, hence the foregoing reasoning would apply to these structures individually rather than to the ovary as a whole. This principle could account for the fact that the two hormones are in some respects antagonistic and in others synergistic in their end effects.

Pregnancy.—Menstruation seems to be contingent upon sudden cessation of ovarian hormone production. This, in turn, results in some unknown way from failure of fertilization of the ovum. If, on the other hand, fertilization does occur, a different train of events ensues. The corpus luteum instead of undergoing regression continues as an actively secreting structure. The endometrium that had been prepared for the process of *nidation* continues its development toward placenta formation. From the fact that after the third week of pregnancy in women destruction of the corpus luteum fails to cause abortion it is obvious either that no further hormone stimulation is needed or that some other source of stimulating hormones comes into action. The available evidence suggests that this source is the placenta. At any rate placental extracts can be separated into fractions of which one is estrogenic and two others possess gonadotropic properties resembling those of anterior pituitary extracts.

When the fertilized ovum reaches the uterus it soon acquires an attachment to that structure. This fixation, nidation, is dependent upon the preceding hypertrophic changes of the endometrium. The outer envelope, the chorion, undergoes rapid development, penetrating the uterine wall and giving rise to the fetal portion of the placenta. According to the best of the evidence the chorionic structures begin to secrete hormone even during the first month of pregnancy and continue this secretion in increasing amounts to the time of parturition. Under its influence together with that of the ovarian hormones and, apparently, of an additional hormone from the anterior pituitary, the various adaptive changes correlated with the pregnancy take place. These changes include modifications of the maternal metabolism to permit the nutrition of the growing fetus and the elimination of the excess waste products of fetal origin. Whether the adaptive mechanisms include changes in the maternal endocrine glands whereby the fetal development is regulated presents an important problem that has been but little studied. The tendency toward thyroid hypertrophy during pregnancy suggests that reactions may occur in other glands. At any rate it is not until the pregnancy is fairly well along toward completion that the endocrine structures of the fetus itself reach a stage of functional efficiency.

The most striking maternal reaction is a continuation of the hypertrophic changes in the uterus itself. The muscular wall undergoes marked increase in bulk, principally by enlargement of the individual muscle cells. Coincident with the uterine changes the walls of the vagina expand and become more vascular and the lubricating secretions increase in amount. Further details

regarding the pelvic alterations during pregnancy may be found in textbooks of obstetrics. The endocrine factors are clearly discussed by Hamblen.[57]

It is not improbable that were technical methods for their quantitative determination available changes in the titer of a variety of hormones in the blood might be detected during the progress of the pregnancy. It is now possible to show that the theelin content of the blood rises progressively from early pregnancy to parturition, at which time the titer is considerably higher than during the premenstrual phase of the sex cycle. Not only is the estrogenic material demonstrable in the blood but the same or a similar active substance is discharged in increasing amounts through the kidneys. Whether, however, the urinary theelin represents true hormone that is formed in excess or whether it is to be regarded as an excretory product is a matter that is still in debate. As previously mentioned, we have only presumptive evidence regarding the precise chemical form in which the sex hormones are discharged into the blood. In any case it can be stated that the excretion of estrogenic material increases from somewhat less than one thousand "mouse units" per liter of urine during the first month to approximately ten thousand units in the last month. The urine of pregnant women is one commercial source of estrogenic material. This high urinary output may be correlated with the relatively great development of the human placenta. In most other primates this organ is relatively much smaller and the renal output of estrogenic material little or none. By injecting suitable extracts of the blood serum of pregnant women into immature mice a marked hypertrophy of their genital tracts can be induced, a fact that is interpreted as indicating an increased maternal production of anterior pituitary gonadotropic hormone. This active substance, too, is discharged in considerable amounts in the urine; it rises progressively to about six thousand mouse units per liter in the fifth month, then gradually declines to about half that amount in the last month of pregnancy. The material ceases to be excreted shortly after parturition.

It is the appearance of these active anterior pituitary-like substances in the urine that makes possible the various tests for pregnancy. In these, mice, rats, or rabbits can be used. The urine itself or a suitable extract is injected and by inspection of the ovaries and the uterine horns of the recipient test animals a day or so later the presence or absence of the stimulating substance can be determined. Positive tests may be secured within the first month of pregnancy. The test is highly reliable but "false positives" may be obtained in certain cases of neoplasm, and particularly in cases of hydatidiform mole.

The evidence regarding the possible relationships of the various other endocrine glands to pregnancy has been discussed at greater length in another publication.[69] The reciprocal maternal-fetal hormone relationships are in need of further study.

It appears, then, that pregnancy is a condition exquisitely dependent upon endocrine factors. The preparatory changes preceding the pregnancy are regulated by the joint action of the ovarian and the corpus luteum hormones and the production of these is in turn dependent upon the influence of pituitary hormone. The inception of pregnancy is dependent upon a degree of normality in both the parents sufficient to assure fertility. After pregnancy is initiated structural changes occur in the pituitary and the thyroid which suggest that

these organs are undergoing compensatory activity. Scanty evidence suggests that adaptive reactions occur also in at least some of the other endocrine glands. The placenta apparently also functions as an endocrine gland producing important regulatory hormones.

Lactation.—The *mammae* are skin glands that have undergone a specialized development. They first become evident in the fetus as a thickening of the skin to form a ridge, the mammary line, extending on each side along the ventral body wall. In many of the mammals the mammary line breaks up into several nodes of development but in the human species ordinarily only a single region toward the cephalic end of each line continues past the rudimentary stage. The occasional occurrence of accessory mammae in women apparently represents a throw-back to the earlier developmental pattern. The proliferation of the growth node results in an inwardly directed sproutlike structure which branches until the total constitutes a fairly complex "duct system." In some species the ducts all converge to a single conducting unit corresponding to the trunk of a tree. In others several branches end independently at the tip of the nipple. In man there are about a dozen such primary ducts. In the further development the ducts enlarge toward their distal ends to form the milk cisterns. The secreting epithelium appears at the terminations of the ultimate branches of the duct system. At the time of birth in the human species only a small amount of such glandular tissue has appeared but enough to permit the secretion of the "witch's milk." Apparently this fluid is formed as a result of the same hormonal stimulation that causes activity in the maternal glands. After severing of the umbilical cord with consequent deprivation of the stimulating hormone the secretion soon ceases.

At birth the mammae of both sexes are similar in structure and stage of development. In males essentially the infantile condition persists throughout life. In girls, however, the onset of puberty is signalled by further development of the mammae. The glandular cells increase in number and size, and fat is laid down in increasing amounts in and around the glandular and duct tissue. The mammae of the adolescent girl, as a matter of fact, consist mostly of fat.

The precise details of the hormonal factors in mammary development in man are as yet largely unknown but there is rather an extensive literature on the relationships in animals from which various plausible deductions can be made as to human conditions.[6, 57]

The prepuberal evolution of the glands comes about chiefly under the stimulating influence of ovarian estrogenic hormone, as is shown by the fact that extirpation of the ovary precludes its occurrence. Since the evolution proceeds to a considerable extent before the onset of corpus luteum formation, hormones from that structure are not primarily involved. It is possible, however, to bring about a considerable development of the mammae in young adult, ovariectomized rabbits by the use of alkaline extracts of the anterior pituitary, hence pituitary hormone presumably plays a significant rôle at this time.

With the onset of pregnancy, the mammary glands, which had reached a resting stage after the puberal evolution, undergo renewed activity. The secretory epithelium further proliferates and at the end of pregnancy the cells are well charged with the precursor substances from which the milk is

formed. During this phase of development the corpus luteum presumably plays a significant, stimulating rôle. In animals, through the successive administration of the estrogenic and the corpus luteum hormones, mammary development can be carried to the lactation phase either in immature females or in males. The burden of the evidence, however, is to the effect that the final stage of lactation, i.e., the breaking down of the mammary cells and the dilution of their contents with water from the blood, is, primarily, if not exclusively, under the control of the special anterior-pituitary hormone, prolactin. The fact that in women amenorrhea is of frequent occurrence during the first few months of lactation suggests that prolactin may have an inhibitory effect on hormone production in the ovary. At the conclusion of the nursing period the mammae revert to approximately the late puberal condition.

At the conclusion of the reproductive epoch in women the mammary glands undergo considerable atrophy. To what extent this is merely a special phase of generalized tissue regression and to what extent it represents a waning of hormonal secretion have not been satisfactorily determined.

The Menopause.—The active reproductive period in women terminates at approximately the forty-seventh year, in the menopause or climacteric. In the individual case this may occur a few years earlier or a few years later than forty-seven.

The manifestations of the menopause are quite variable. In some instances the onset is insidious and the transition is marked only by increasing irregularity of menstruation until it finally ceases; in other cases the onset is abrupt. The climacteric may be accompanied by few perturbations or by such distressing symptoms as irritability, difficulty in concentration, mental depression, restlessness, and insomnia. These manifestations may become so marked as to constitute the psychosis, involutional melancholia. The symptoms may be of brief duration or may persist for months or years; they may be recurrent with intervals of approximate normality. The participation of the sympathetic nervous system in the production of the symptoms of the menopause, especially the "hot flashes," was mentioned in an earlier paragraph. Although the usual course of onset is a gradual lessening of the menstrual flow the climacteric may be ushered in by a period in which profuse flow occurs.

The menopausal picture ensues when the ovaries are removed at any time after puberty is established, and it can be induced by the application of radium to the ovaries. The symptoms of the induced menopause are likely to be more acute and abrupt in onset than when the condition arises spontaneously. The primacy of ovarian failure in the causation of the symptoms is indicated by their prompt onset after ovariectomy. Whether other endocrine structures participate significantly has not been satisfactorily determined. Some authors report evidences of overactivity of the thyroid gland at this time, but others have found precisely the opposite condition. The fact that the basal metabolic rate ordinarily shows no significant depression rather points toward the absence of thyroid deficiency as a contributory factor.

A tendency toward masculinization at the climacteric has often been noted. This is indicated by increased growth of hair on the face and especially on the upper lip, a lowering of the pitch and a change in the timbre of the voice, and perhaps a significant degree of change in the temperament. These

tendencies suggest accentuated function of the adrenal cortex, but satisfactory objective evidence of this is lacking. In view of the intimate relationship between the ovaries and the anterior pituitary it might be anticipated that the latter would undergo significant morphological changes at this time. Such, apparently, is not the case. The functional evidence, however, is somewhat more indicative of coincident change in hypophyseal activity. In a considerable proportion of women it has been possible to demonstrate an increased amount of the follicle stimulating hormone in the blood and it occurs rather regularly in the urine. The occasional occurrence of mild acromegalic changes at the menopause may be construed as further evidence of overactivity of the anterior pituitary.

The evidence regarding the utility of ovarian preparations in the alleviation of the climacteric symptoms is notably lacking in consistency. The element of suggestion demonstrably can play an important rôle and in many of the studies that have been reported suggestion has not been adequately excluded as the chief or only cause of improvement. Since the purified active principles have become available, however, the evidence has become somewhat more convincing. Thus Werner and his associates[140] in an extensive and well-controlled series of clinical experiments have reported marked amelioration even when the symptoms have reached the severity characteristic of involutional melancholia.

From the fact that the nervous manifestations of the menopause gradually cease it would appear that the symptoms are due rather more to a hormonal imbalance than to ovarian deficiency, as such. For a more extensive discussion of this and similar topics Mazer and Goldstein,[98] and Hamblen[57] may be consulted.

Sterility.—Sterility may be due to any functional or mechanical condition that prevents the introduction of spermatozoa into the vagina or access of these gametes to the ovum. Similarly, nutritional or other abnormalities that prevent the formation of viable gametes will cause sterility. For the operation of the various nonendocrine factors the textbooks of gynecology may be consulted. This discussion will deal only with the hormonal abnormalities that may prevent either conception or the development of the fertilized ovum.

It should be emphasized that infertility is a relative condition. Numerous cases are on record of sterile matings in which both partners were subsequently proved to be fertile. Infertility ranges in the various cases from slight to absolute. If both parties to a given mating are highly fertile, pregnancy results promptly and repeatedly, unless effective contraceptive measures are employed. If both are of relatively low fertility the matings will be either entirely unfruitful or only occasionally successful.

Infertility may be due to incomplete development of the reproductive organs or to a secondary decrease in the vitality of the gametes. In women, actual persistence of the early juvenile conditions is relatively rare, but in many cases development halts at the pre-adult stage. The common cause of this halting, according to Meaker,[99] is relative deficiency of either the pituitary or the thyroid gland at the hebetic epoch. This period having passed, the deficit seems to be overcome and, adult years having been reached, no further signs of hormone deficiency may be evident. But the underdevelopment of the reproductive organs tends to persist as a permanent handicap to fertility. Ovula-

tion may fail entirely or be infrequent; likewise, the ova that are discharged may be incapable of being fertilized. In men, comparable persistence of juvenile conditions is usually not objectively evident but the spermatozoa that are produced may be of such low viability as seldom or never to complete a normal fertilization. In Meaker's experience the most common endocrine disorder that causes sterility in women is deficiency of the anterior pituitary. Evidences of this abnormality were found six times as frequently as those of primary ovarian deficiency. Thyroid deficiency occupied a middle ground. Statistics on the relative frequency of similar glandular defects in men are not available. Attempts to correct infertility by endocrine medication have been most successful from the use of thyroid substance. Potent gonadotropic pituitary extracts have not been available for a sufficient period to permit the accumulation of definite statistics on their value. Ovarian preparations have proved to be of relatively little use.

CHAPTER LXXVII

PINEAL, THYMUS AND OTHER POSSIBLE ENDOCRINE ORGANS

THE PINEAL GLAND

Despite a great deal of investigation the status of the pineal gland as an endocrine structure remains somewhat indeterminate. In some vertebrate species it seems to be merely a vestigial organ, while in others it is a fairly distinctive morphological structure. Microscopically, it presents relatively little evidence of having a secretory function. It is made up largely of supporting tissue, but it contains a considerable amount of pigment, some lipoid material and, in some species at least, shows cells that bear a resemblance to secreting epithelium. In many forms it has a rich blood supply which suggests the possession of functional activity.

Many negative results have been secured from the administration of *pineal extracts*. When injected directly into the blood stream such materials cause a fall of blood pressure and sometimes passing polyuria, but since similar results may be obtained from indifferent tissue extracts, they have slight weight as evidence of hormonal function.

Recently Hanson has succeeded in making an acid extract of pineal tissue which, in the hands of Rowntree and his associates,[118] has yielded somewhat striking results. The extract was administered intraperitoneally each day to successive generations of parent rats, and the effects upon both parents and offspring were noted. Following its use, breeding occurred more frequently and, in succeeding treated generations, both the birth-weight and the rate of growth were increasingly depressed, but the rate of differentiation and development was accelerated. In the fifth generation of treated animals the average young rat was of less than half normal weight, was sexually mature at approximately half the normal time and evidenced marked precocity in the development of fur, eruption of the teeth, and opening of the eyes. These results are set forth as representing true experimental *dwarfism*. The fact that the influence of the extract was cumulative through succeeding generations represents an unusual biological happening and suggests the necessity of accumulating more than the ordinary weight of evidence. The offspring showed diminution of general vitality as indicated by high mortality rate and lack of vigor, but in some instances the frequency of littering was remarkable, the interval between litters being as short as twenty-three days. As to the effect of the Hanson extract in human subjects no data have as yet been reported. There is a clinical condition which is marked by persistence of growth well beyond the normal age of maturity and accompanied by lag of sexual development. For this condition a hormone having the properties reported for pineal extract would offer considerable promise of clinical usefulness.

Pineal feeding in the hands of most investigators has given equivocal or negative results, though McCord[88] reported a generation ago that the develop-

ment of puppies was somewhat accelerated by the administration of desiccated gland substance from calves. That such material is not entirely devoid of physiological potency is indicated by the results of McCord and Allen[89] who added desiccated pineal substance to the water in which tadpoles were kept. This caused a sharp contraction of the melanophores, giving the animals a strikingly peculiar silvery translucent appearance. The observations have been confirmed by Addair and Chidester[2] who added the observation that metamorphosis was hastened.

Pinealectomy has commonly given negative results. The operation is difficult and the mortality is high. Izawa,[75] however, confirming the positive results of a few earlier observers, reported that destruction of the pineal resulted in accelerated development in rats of both sexes. Two months after the operation the gonads were found to be approximately a fourth larger than in the control subjects.

Some further evidence on the presumptive endocrinology of the pineal is derived from the study of the clinical condition, *macrogenitosomia praecox*. Although the disorder has been written upon at length, the actual recorded number of proved cases is rather small; Haldeman[56] in 1927 was able to find accounts of but sixteen. All occurred in males and the disorder was first detected in the various instances from the ages of three to sixteen years. It was marked by a precocious development both of the body and of the sex organs. In a typical instance a five-year-old subject was described as a "Hercules in miniature," burly in figure with the low-pitched voice, beard, and sex organs of an adult. A somewhat comparable degree of mental maturity has been occasionally reported. In addition to the proved cases a considerable number have been reported in which pineal involvement was presumptive only. Whether the association of precocity with pineal tumor indicates a genuine hormone function or whether the precocity is due merely to the mechanical influence of the neoplasm on contiguous nervous structures has been much debated without reaching unanimity of opinion. The evidence, on the whole, is inconsistent. Izawa's work suggests that deprivation of the gland releases the developmental potential of the animal, whereas pineal tumors, supposedly productive in type, seem to have a similar effect. The Hanson extract caused depression of growth but acceleration of sexual development. Obviously more evidence is needed.

THE THYMUS GLAND

A somewhat similar lack of definite evidence confronts one in a consideration of the literature on the thymus. That animals can survive in good health complete extirpation of this organ has been abundantly proved. On the other hand, animals lacking the gland seem to be abnormally sensitive to environmental stresses and particularly to malnutrition or suboptimal vitamin intake. Under the combined influence of *thymectomy* and unfavorable environmental conditions a generalized stunting has frequently been reported, with failure of mineralization of the bones as an outstanding feature. The subjects are apathetic and in some cases have been reported to show a condition comparable to imbecility in man.

In the literature two correlations stand out with rather impressive consistency, namely, thymus enlargement following *castration* and a similar hyper-

trophy under conditions in which diminution of the adrenal cortical function occurs. Grollman[53] has noted the consistent occurrence of *status thymico-lymphaticus* in chronic *adrenal deficiency*. This coincidence acquires special weight from the fact that the thymus is a labile structure that atrophies quickly under most conditions of malnutrition, whereas malnutrition is a prominent feature of adrenal deficiency. Presumptive evidence of an antagonistic relationship between the gonads and the thymus is seen in the fact that the latter structure achieves its maximum relative weight during the prepuberal period and then recedes as the gonad hormones begin to function prominently.

Several investigators have reported that *thymus feeding* causes a marked change in the metabolism of tadpoles. Metamorphosis and sexual development are markedly delayed and overgrowth during the persistent larval stage occurs. Some investigators have regarded this merely as a nutritional phenomenon but Gudernatsch[55] who has extensively reviewed the literature believes that a thymic hormone is involved. Riddle[112] has observed that doves having diseased thymus glands have a marked tendency to produce eggs with defective shells and that the disorder can readily be corrected by thymus feeding.

More recently Asher and his collaborators[11] have contributed extensive observations on the influence of an aqueous *thymus extract* which has produced significant acceleration of growth and development. It overcame the loss of weight in rats subjected to vitamin lack and caused hypertrophy of the gonads.

Recently extensive studies have been reported by Rowntree[117] who adds to a review of the preceding literature an account of the work done by himself and collaborators with a thymus preparation evolved by Hanson. The material is an acid-aqueous extract of the neck thymus of young calves. Injections of this extract led to augmentation of weight, more frequent breeding, and production of larger litters of heavier-than-normal offspring. When the treatment was continued through several generations a cumulative effect was seen, each generation showing successively greater acceleration in growth and development as well as sexual precocity. In a subsequent publication Einhorn and Rowntree[37] have reported that thymectomy in succeeding generations has an effect the reverse of that of the thymus extract; there occurred a retardation of development which, however, was spontaneously normalized after seventy days of age. Subsequently these reported effects of thymus extract and of thymectomy have failed of confirmation at the hands of other investigators.

Hypertrophy of the thymus in infancy is a clinical condition encountered frequently in some parts of the world but rarely in others. This may lead to mechanical interference with respiration and has been reported to be associated with abnormal vulnerability of the subjects to anesthesia and trauma. In the field of pediatrics an extensive and somewhat controversial literature on the subject exists. What significance, if any, such manifestations may have in relation to the hormone physiology of the thymus is not evident.

The total weight of the data now available suggests that the thymus has a significant influence upon growth and development and upon sexual maturity but that under favorable environmental conditions the individual is able to dispense with the thymic function without significant detriment to health. Whether the phenomena reported indicate the secretion of a true thymus hormone or whether the relationships are mediated in other ways is by no means certain.

OTHER HORMONES

The *pancreas* by virtue of its contained islands of Langerhans is an important endocrine organ but since the hormone relationships are intimately bound up with carbohydrate metabolism they are treated in the section devoted to that subject (Chapter LI).

The motor and secretory *digestive functions* are likewise in considerable measure subject to hormone control and discussion of the various hormones involved will be found in the chapters devoted to digestion.

In addition to the hormones produced by the various endocrine glands, researches of recent years have disclosed also the existence of what might be designated as special *tissue hormones.* Two are involved in the mediation of nervous impulses and are discussed in connection with the physiology of the autonomic nervous system. They are *acetylcholine* and *sympathin.*

PART VIII

THE DISTRIBUTION AND REGULATION OF WATER IN THE BODY

By Magnus I. Gregersen

CHAPTER LXXVIII

DISTRIBUTION OF WATER

Water is by far the largest single constituent of the body. Claude Bernard endeavored to calculate the proportion of water in the human body by comparing weights of Egyptian mummies with the weights of living individuals of the same size and shape, but his figures (90 per cent) are too high for the reason that prolonged desiccation is attended also by the loss of solid substances. Actual measurements have been made by drying the tissues until there is no further loss in weight. At a temperature of 100-105° C. there is no charring of the tissues and probably very little loss of anything but water. Using this method, Bischoff in 1863 determined the water content of a fresh corpse (executed criminal). His values are tabulated in Table CIX.

Table CIX

(From Siebeck[119])

Body	70 Kg.	Water Content 59% = 41.0 liters
Muscles	30 Kg. = 42% of B.W.	Water Content 76% = 22.8 liters
Fatty Tissues	13 Kg. = 18% of B.W.	Water Content 30% = 3.8 liters
Skeleton	11 Kg. = 16% of B.W.	Water Content 22% = 2.4 liters

From this and subsequent investigations on man and animals, Skelton[120] has compiled results which show that corresponding organs in different species contain approximately equivalent proportions of water (Table CX). Warm-

Table CX

Percentage of Water in Organs in Relation to Their Weight (From Skelton[120])

ORGANS	MAN	RAT	DOG	CAT	RABBIT
Skin	72.03	77.1	58.9	68.3	71.4
Muscles	75.67	76.2	73.5	74.5	75.08
Skeleton	22.04	47.4	31.66	32.8	20.54
Brain	74.84	77.5	75.03	78	77.93
Spinal cord	----	69.13	69.53	----	69.42
Liver	68.25	74	73.7	67.9	75.8
Heart	79.21	77.6	78.39	78.46	78.58
Lungs	78.96	81.6	78.7	76.3	77.65
Kidneys	82.68	77.1	76.72	75.3	78.86
Spleen	75.77	77.4	78.6	78.2	80
Blood	83	80.82	82.8	86.7	82.8
Intestine	74.54	76.36	75.4	78.3	78.4
Entire body	63	65.3	65.7	64.2	68.8

blooded animals seem to have a general similarity both in the total percentage of water and in its anatomical distribution. Nevertheless, the percentage of water in the body may vary considerably among individuals of the same species. It is affected by the quantity of adipose tissue present, since fat is laid down with relatively little water, as illustrated by Bischoff's figures. It varies also with age, gradually decreasing after the first six months. In addition, there are numerous other factors about which our knowledge is limited (diet, endocrines, etc.) that undoubtedly modify the percentage of water under so-called normal conditions. Table CXI shows that the percentage weights of the

TABLE CXI

PERCENTAGE WEIGHT OF ORGANS IN RELATION TO BODY WEIGHT (FROM SKELTON[120])

ORGANS	MAN	RAT	DOG	CAT	RABBIT
Skin	18	18.01	16.11	13.94	13.2
Muscles	41.7	45.4	42.84	45.36	52.2
Skeleton	15.9	10.9	17.39	12.67	12.4
Brain	2.01	0.46	1.37	1.04	0.58
Spinal cord	----	0.16	----	0.07	0.18
Liver	2.26	4.17	3.6	2.96	5.2
Heart	0.47	0.34	0.81	0.37	0.88
Lungs	0.69	0.53	0.88	0.51	1.24
Kidneys	0.37	0.78	0.65	0.81	0.71
Spleen	0.18	0.25	0.22	0.28	0.1
Blood	4.9	5.5	7	4.46	6.75
Intestine	1.81	3.96	6.5	3.8	4
Rest of body	4.63	2.89	2.63	4.1	1.88

different organs in relation to total body weight are essentially the same for man, dog, rabbit, cat and rat; and Table CXII gives the actual amount of water located in various organs and tissues of the body. By far the largest amount is found in the skeletal muscles and skin. This feature is important in connection with the functions of these two tissues as storehouses for water.

TABLE CXII

DISTRIBUTION OF WATER TO VARIOUS ORGANS AS COMPUTED FROM VALUES SET FORTH IN TABLES CX AND CXI WHEN BODY WEIGHTS ARE: MAN, 65 KG.; RAT, 450 GM.; DOG, 4 KG.; CAT, 2 KG.; RABBIT, 2.5 KG. (FROM SKELTON[120])

	MAN		RAT		DOG		CAT		RABBIT	
ORGANS	O. W.	G. W.	O. W.	G. W.	O. W.	G. W.	O. W.	G.W.	O. W.	G. W.
Skin	11,700	8,437.5	81	62.45	644.4	379.5	278.8	190.4	330	235.6
Muscles	27,105	20,510	204	155.6	1,713.6	1,259	907.2	675.8	1,305	979.7
Skeleton	10,335	2,277	49	23.2	695.6	220.2	253.4	83.1	310	63.6
Brain	1,306	977.7	2	1.6	54.8	41.1	20.8	20.5	14.6	11.3
Spinal cord	-----	-----	0.7	0.5	----	----	5.4	----	4.7	3.2
Liver	1,469	1,002.5	18.7	13.8	144	106.1	59.2	40.1	130	98.5
Heart	305.5	241.9	1.5	1.1	32.4	25.3	7.4	5.8	22	17.2
Lungs	448.5	354.1	2.3	1.9	35.2	27.7	13.8	10.5	31	24
Kidneys	240.5	198.8	3.5	2.7	26	19.9	7.4	5.5	17.7	13.9
Spleen	117	88.6	1.1	0.9	8.8	6.9	5.6	4.3	2.5	2
Blood	3,195	2,651	24.7	20	280	231.8	89.2	77.3	168.7	139
Intestine	1,176.5	876.9	17.8	13.6	260	196	78	59.5	100	78
Rest of body	-----	6,046	----	6.1	----	114	---	11.4	----	51.3
Total		40,950		293.8		2,628		1,284		1,171

O. W. indicates weight of organ in grams; G. W., grams of water in the organ.

The desiccation method for determining the water content of the body has the serious drawback that the determination itself constitutes a terminal experiment, and recent years have therefore seen several attempts to devise techniques that can be utilized in the intact animal and in man. Under appropriate conditions the total body water may be calculated from changes in the concentration of serum electrolytes brought about by the administration of a large quantity of salt or water.[42, 59, 65, 81] According to Painter's recently published work,[103] total body water can also be determined, at least in the dog, with urea or sulfanilamide, for she finds that the body water available for the solution of either of these two substances is the same, within experimental error, as the total body water determined by subsequent desiccation. Incidentally, her observations confirm the now generally accepted conclusion that the amount of "bound water" in the body is relatively insignificant. (See footnote, page 1085.)

When the total amount of body water is altered by adding or withdrawing fluid through the blood stream, all tissues are not affected equally. The capacity of various tissues to take in or give up fluid varies to a considerable degree and is influenced by associated changes in the electrolyte balance. Engels[26] observed that when he gave large intravenous injections of physiological salt solution to dogs, all the tissues except the bone became more watery; the muscles took up most of the injected fluid (67 per cent). His results, however, are open to the criticism that no control observations were made on the injected animals themselves.

More direct evidence is provided by Skelton's experiments on cats in which samples were taken from corresponding tissues of the same animal before and after it was bled or given an intravenous injection of one of several solutions. After severe hemorrhage (15 ml. per kg. body weight), the blood became more watery at the expense of all other tissues examined. Table CXIII shows the pro-

TABLE CXIII

SOURCE OF FLUID ENTERING BLOOD STREAM EXPRESSED IN PERCENTAGE OF AMOUNT COMING FROM VARIOUS TISSUES (FROM SKELTON[120])

CAT	SKIN	MUSCLE	LIVER	INTESTINE	SPLEEN
1.	9.3	14.9	3.3	3.4	0.13
2.	12.7	14	3.8	3.8	0.03
Average	11	14.45	3.5	3.6	0.08
3.	38	16	8.3	3.1	0.34
4.	49	16	8.4	2.1	0.42
Average	43.5	16	8.35	2.6	0.07
5.	30	45.2	10.4	0.74	0.72

portion of the total water which entered the blood from various tissues, and Table CXIV the amount of fluid given up per 100 Gm. of tissue. In his cats 1 and 2 which had no previous treatment, the muscles supplied somewhat more fluid than the skin; but in animals 3 and 4 which had been given no food or fluid for 32 and 72 hours, respectively, the skin was by far the most important source of fluid, and also gave up more water per 100 Gm. of tissue than any other organ. Although the muscles contain two and one-half times as much water as the skin, the latter competes with the muscles as a storehouse for water by virtue of the fact that it may undergo much larger changes in its percentage of water.

Skelton's results with injections of water (25 ml. per kilogram) and hypo-, iso- and hypertonic solutions of sodium and calcium chloride (20 ml. per kg.) are included in Table CXV. We see that in the case of water and hypotonic sodium chloride solution, the muscles and the liver took up most of the water, whereas with isotonic and hypertonic sodium chloride the fluid went mainly to the skin, the muscles either undergoing no change or actually losing water. Padtberg[102] believed that the skin has a special function in relation to the storage of sodium chloride. After intravenous injections of this salt, as much as 77 per cent of the amount retained was found in the skin; and when animals were kept on a chloride-poor diet, the skin provided from 60 to 90 per cent of the total chloride lost from the body. There is also evidence that the skin can store salt, at least temporarily, with less than enough water to dilute it to isotonicity. If large amounts of salt are taken by mouth, only a portion is excreted at once; the location of the retained chloride is indicated by the edema of the skin which is produced when a large amount of water alone is subsequently ingested. Sodium chloride not only directs the water to the skin, but tends to hold it in the body.

TABLE CXIV

AMOUNT OF FLUID GIVEN UP BY 100 GM. OF TISSUE FOLLOWING HEMORRHAGE (FROM SKELTON[120])

CAT	SKIN	MUSCLE	LIVER	INTESTINE	SPLEEN
1.	1.2	0.6	2.2	1.9	1
2.	1.2	0.4	2	1.3	0.6
Average	1.2	0.5	2.1	1.6	0.8
3.	3.2	0.4	3.2	0.9	3.3
4.	4	0.39	3.2	0.7	2.17
Average	3.6	0.4	3.2	0.8	2.73
5.	2.1	0.9	3.2	1.75	0.25

The difference observed by Skelton in the effects of sodium and calcium chloride in corresponding concentrations (Table CXV) is referable to the fact that calcium is much less diffusible than sodium. This is shown by the more persistent hydremia and by the movement of fluid from all the tissues into the blood when the hypertonic (2.4 per cent) solution was injected. In the latter case, the skin was again the most important source of fluid.

The general implication of these experiments is that the water content of the blood and other vital organs is to a large extent preserved at the expense of changes in the fluid content of the muscles and the skin. Other tissues, such as the liver and intestines, also play an important role, especially in taking care of sudden changes; but because of the relatively smaller mass of these organs in comparison with muscle and skin, they handle correspondingly smaller quantities of fluid.

The capacity of various organs to function as fluid reservoirs appears to be conditioned by the amount of loose connective tissue which they contain. As described above, it was from the skin, in which this form of histological structure with large intercellular spaces is particularly prominent, that Skelton found the largest fluid loss per 100 grams of tissue after injection of hypertonic $CaCl_2$. Organs consisting mainly of parenchyma are said to show

TABLE CXV

CHANGES IN THE WATER CONTENT IN VARIOUS ORGANS FOLLOWING INTRAVENOUS INJECTION OF WATERY SOLUTIONS (FROM SKELTON[120])

	DISTILLED WATER		0.45% SODIUM CHLORIDE		0.9% SODIUM CHLORIDE		1.8% SODIUM CHLORIDE		0.6% CALCIUM CHLORIDE		1.2% CALCIUM CHLORIDE		2.4% CALCIUM CHLORIDE	
	A	B	A	B	A	B	A	B	A	B	A	B	A	B
Blood	23.7	17	37.26	20	49.45	27.7	59.3	33.7	64.4	36.1	74.5	41.8	100 +	
Muscle	13.1	0.75	21.70	1.3	0	0	Loss	−1.2	16.4	1.1	Loss	−4.3	Loss	−0.5
Liver	9.5	7.6	5.57	4.6	3.91	4.3	3.45	4.1	5	3.0	3.2	2.4	Loss	−2
Skin	5.8	1.1	11.1	1.9	13.57	4.5	17.5	4.8	8.1	1.14	Loss	−3.55	Loss	−4.2
Intestine	2.7	2.1	4.5	2.8	2.21	1.9	2.81	1.9	2.6	1.33	3.9	2.6	Loss	−0.6
Spleen	0.16	1.6	0.09	0.9	0.07	0.9	0.09	0.9	0.18	0.87	0.26	2.4	0	0

Under A are listed the percentages of the injected fluid remaining in the blood stream or absorbed by the various tissues at the end of thirty minutes; under B, the grams of fluid taken up or lost (—) by 100 Gm. of tissue.

The results with distilled water are an average of six experiments: with 0.45% sodium chloride, 8; 0.9% sodium chloride, 8; 1.8% sodium chloride, 6; 0.6% calcium chloride, 6; 1.2% calcium chloride, 6; 2.4% calcium chloride, 4.

no appreciable loss of water in severe dehydration.* From these and other observations the belief has arisen that the intercellular spaces serve as a reservoir of fluid for sustaining the plasma volume.[38]

There can be no doubt that this concept is correct, for in dehydration, for example, the actual decrease in volume of the plasma constitutes but a small fraction of the total loss in the body. As the body gives up water to the external environment, it also draws upon the fluid stores in the adjacent interstitial spaces. But this does not mean that the plasma volume is maintained at a constant level in the face of a large depletion of the total body water. On the contrary, it has been the experience of the writer, based on results obtained with suitable methods for estimating changes in volume of the body fluids (see pages 1067-1071), that in dehydration the per cent shrinkage in the plasma volume is considerably greater than that observed in the interstitial fluid.[52] This is illustrated by Table CXVI showing the results of a typical ex-

TABLE CXVI

SHOWING THE EFFECTS IN THE SAME DOG OF TWO PERIODS OF FOOD AND WATER DEPRIVATION

DATE	BODY WEIGHT	PLASMA VOLUME		"AVAILABLE FLUID"
		CALCULATED FROM PLASMA PROTEIN	DETERMINED WITH T-1824	DETERMINED WITH NaSCN
	% change	% change	% change	% change
Oct. 6-17, 1938	−13%	−1.7%	−30%	−15%
Jan. 11-23, 1939	−15%	−4.8%	−35%	−16%

From data reported by Gregersen and Painter.[52]

periment on a dog subjected to eleven days' water deprivation. It should be noted that this experiment is a glaring example of circumstances in which one would arrive at an entirely erroneous conclusion by assuming that relative changes in plasma volume can always be estimated from the change in plasma protein concentration.

The various studies on the anatomical distribution of water and its relation to the electrolyte exchange have led to a very useful concept of the partition of the body fluids based on function. This is shown diagrammatically in Fig. 365. As a distinct compartment we have the water contained in the vascular system, through which fluid is being circulated rapidly under pressure maintained by the action of the heart. At the bottom lies the intracellular fluid in which the living processes occur. Separating these two is the intercellular or interstitial fluid which surrounds the cells and constitutes the internal environment of the organism. Water enters the system through the small and large intestines and leaves by way of the lungs, skin and kidneys. A small amount is also excreted in the feces. The total water content of the system is determined by the mechanisms which control the passage of fluid through these channels. Since fluid passes in and out of the body only through the plasma compartment, the interstitial and intracellular compartments depend entirely upon the plasma for their supply.

*Kudo's[74] studies on the loss of weight of selected organs in the rat after severe dehydration and inanition do not support these statements. His animals, however, were dehydrated and starved until they lost approximately one-third of their weight and it may well be that this condition is too extreme to display any selective loss of the interstitial fluids.

The problem of water balance, therefore, presents two main aspects which are closely related: 1, the exchange between plasma and the outside; i.e., the total water exchange of the body; 2, the exchange between plasma and the interstitial and intracellular compartments. Inasmuch as the walls of the fluid compartments are elastic, the mechanisms which control the volume of water in the entire body and its separate compartments are complicated and must be delicately balanced. These mechanisms are our chief concern, but before discussing them it is advisable to gain some idea of the composition of the body fluids and the actual amount of water distributed in each of the three compartments.

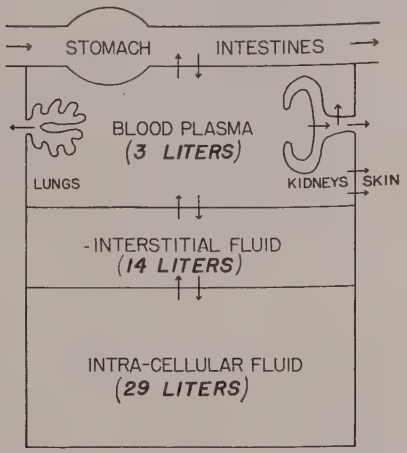


Fig. 365.—Gamble's diagrammatic illustration of the three fluid compartments. The figures in parentheses have been inserted by the author to show the volume of water in each compartment of a subject weighing 70 kg. whose total water content is assumed to be 46 liters (two-thirds of the body weight). (Modified from Gamble.[39])

COMPOSITION OF FLUID IN THE VASCULAR, INTERSTITIAL AND INTRACELLULAR COMPARTMENTS

Detailed information on the composition of the various body fluids may be found in textbooks of biochemistry. For the purposes of the present discussion, it is sufficient to consider diagrammatically the ionic concentrations of the important constituents in the three fluid compartments, as in Fig. 366.

The composition of the vascular compartment is given by the analysis of serum. The erythrocytes are not included, for they form a rather specialized part of the intracellular compartment. The composition of interstitial fluid is represented approximately by the second and third diagrams, constructed from analyses of lymph and cerebrospinal fluid, which are believed to have nearly the same composition as true interstitial fluid. The latter does not under normal conditions accumulate in sufficient quantity to be collected for analysis, but Maurer[93] has succeeded in obtaining small amounts of true extracellular muscle fluid from the frog. The composition of intracellular fluid is also a matter of some uncertainty, since it is impossible to remove the interstitial fluid dispersed among the cells; but the important chemical features of the intracellular compartment are shown by the analysis of muscle. The assumption which apparently best fits experimental facts is that the intracellular fluid contains only a small amount of sodium and no chloride.[61]

From Fig. 366 it is evident that except for the difference in protein content the plasma and interstitial fluids are practically identical. In both, the base is almost entirely made up of sodium, the acid largely of chloride and bicarbonate. The barrier which separates the two compartments is therefore

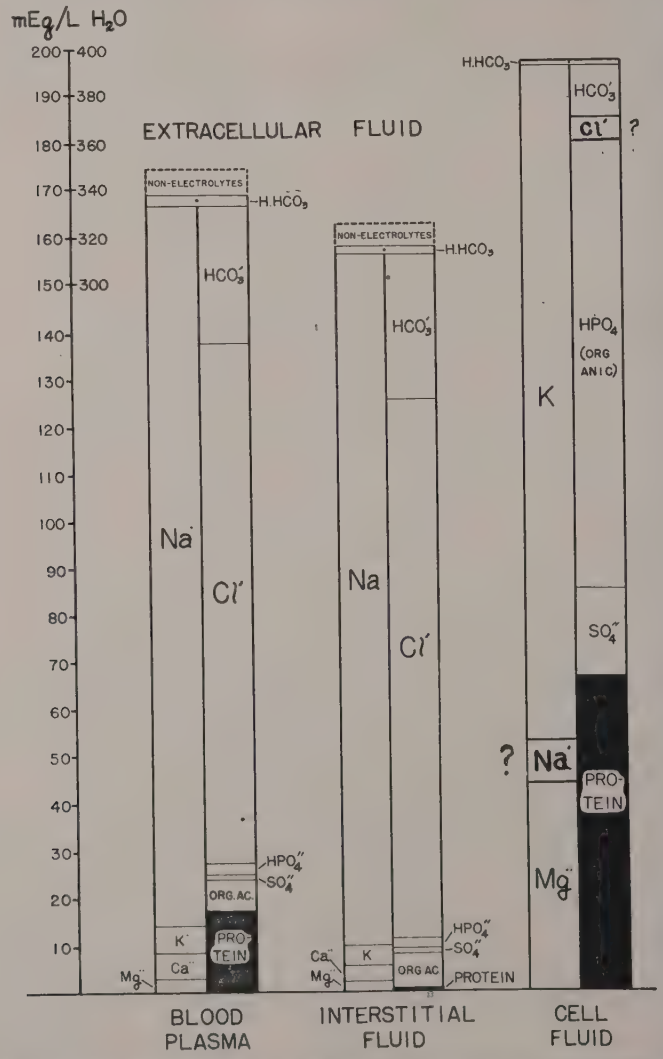


Fig. 366.—Diagram showing the chief chemical constituents of the three fluid compartments. The height of the left half of each column indicates the total concentration of cations, that of the right half, the concentration of anions. Both are expressed in milliequivalents per liter of water. Note that the chloride and sodium values in cell fluid are questioned. It is probable that at least in muscle the intracellular phase contains some sodium but no chloride. (Modified from Gamble.[87])

permeable to all constituents except the protein, a situation which gives rise to a slightly higher chloride and lower sodium concentration in the interstitial fluid than in the plasma (Gibbs-Donnan effect).

The intracellular fluid presents a very different picture. Here we find potassium as the predominant base and no chloride among the anions, showing that the barrier between the interstitial and intracellular compartments is endowed with a high degree of selective impermeability. This is further illustrated by the unequal distribution of phosphate. From the point of view of chemical structure, therefore, intracellular fluids are entirely different from the extracellular fluids, whether in plasma or intercellular spaces.

VOLUME OF FLUID IN THE VASCULAR, INTERSTITIAL AND INTRACELLULAR COMPARTMENTS

The Vascular or Plasma Compartment.—Of the three fluid compartments, the vascular is the smallest but in many respects the most important. It is the link between the internal and external environments, the sole channel of exchange for all substances which reach the cells and are carried away from them. By virtue of the fact that it circulates rapidly through every portion of the body, it endows the tissue fluids bathing the cells with the same constancy of composition which in the plasma itself is jealously guarded by innumerable mechanisms. In order to carry out this function effectively, the plasma must maintain its volume as well as its composition. More than that, the volume, through its effect upon capillary pressure, is a potent factor in deciding the direction of fluid exchange between plasma and tissue fluid. The body keeps the plasma volume constant with great persistence, a fact which suggests that changes in the plasma volume are in themselves responsible for setting in operation the mechanisms which exist for its regulation. Such an arrangement presents obvious advantages to the organism, since any influence of the external environment upon the fluid balance is first made known in the vascular compartment.

The plasma volume may be determined by injecting a known amount of some nontoxic, nondiffusible foreign substance intravenously and measuring the extent to which it is diluted when thoroughly mixed with the circulating blood. Among the substances which have been used for this purpose may be mentioned gum acacia, foreign serum, hemoglobin and a number of vital dyes (vital red, brilliant vital red, congo red, trypan blue, trypan red, T-1824 and others). The aim has been to select a substance which escapes very slowly from the blood stream, which is not taken up by the red cells, is soluble and stable in the plasma, and which can be determined accurately and conveniently in plasma or serum samples. For the last reason in particular, dyes have been most popular since their concentrations can be estimated colorimetrically. The use of dyes for measuring plasma volume was introduced in 1915 by Keith, Rowntree and Geraghty.[71] For description and criticisms of their technique and of the many subsequent modifications of the dye-dilution method, the reader is referred to the articles by Erlanger,[27] H. P. Smith,[123-125] Seyderhelm and Lampe,[115] Griesbach[56] and Gregersen, et al.[44, 49, 50, 54, 55] Of the mass of data which has accumulated, so much conflicts on grounds purely technical that it is desirable to consider briefly some of the chief sources of error in the method.

The determination of the concentration of dye in a sample of plasma or serum may be complicated by the fact that the solvent itself is not water clear or colorless. Keith, Rown-

tree and Geraghty[71] attempted to cancel natural plasma color by reading the unknown (dye-stained plasma obtained after the dye injection) against a standard prepared by adding a measured amount of the dye solution which was injected to a sample of control plasma (taken just before injection). Both samples were diluted to the same extent to maintain equal concentrations of the original plasma constituents. Even this precaution does not insure a correct determination in a simple colorimeter unless the dye concentrations happen to be identical in the two samples, i.e., unless the fields match when the plungers are set at the same height (R = 100). If this condition is not fulfilled and the circulating plasma is highly colored with dye left over from a previous determination (residual dye), the error in estimating the increase in plasma color resulting from a single injection may be very large (30 per cent). The nature of this difficulty is seen from the equation:[123]

$$\frac{R_3}{100} = \frac{R_1 + R_3}{R_2 + 100}$$

in which R_1 is the residual dye, R_3 the increase in dye concentration of the plasma caused by the injection, and R_2 the actual colorimetric reading. This shows that the value R_3 which must be used in calculating the plasma volume is not the same as the actual colorimetric reading R_2 unless R_1 is equal to zero or unless R_2 is equal to 100. Furthermore, it shows that the discrepancy between R_2 and R_3 depends upon whether R_2 is higher or lower than 100. Therefore, the estimated plasma volume may be too high or too low depending upon the relative concentration of the standard and unknown. This is shown by the following experiment, the results of which are presented in Table CXVII.

TABLE CXVII

REPEATED DETERMINATIONS OF PLASMA VOLUME (DOG) WITH THE KEITH-ROWNTREE METHOD SHOWING THE RESULTS OBTAINED WITH STANDARDS OF DIFFERENT STRENGTHS

STANDARD (DILUTION OF ORIGINAL DYE SOLUTION)	PLASMA VOLUME IN ML.				RATIO OF UNKNOWN / STANDARD
	1ST	2ND	3RD	4TH	
1-300	925	925	930	910	R = 100
1-200	—	780	710	670	R > 100
1-400	—	1075	1115	1150	R < 100

The plasma volume of the dog was determined four times in the course of a few hours by the dye method as described by Keith, Rowntree and Geraghty. In each case, the unknown was read against *three* standards of different strengths, and the plasma volume calculated from each of these readings. It is evident that the same result was obtained only when the unknown was read against a standard of equal strength (R = 100). As the residual dye concentration increased after each injection, the other results were progressively higher or lower than the true volume, depending upon which standard was used. Thus one may account for the inconsistent values reported by certain investigators who have used the Keith-Rowntree technique for repeated determinations.[76]

Theoretically, the compensating colorimeter should eliminate the difficulties with residual dye and natural plasma color. The important feature of this instrument is that optical symmetry is maintained no matter how different the standard and unknown happen to be; but for reasons which are not clearly understood, this colorimeter fails to yield dependable results. Furthermore, it cannot be used if the plasma samples show any lipemia or if samples are hemolyzed. It should be noted also that in analyses with the compensating colorimeter, a number of investigators have introduced systematic errors into their determinations by comparing the unknown with standards made up in water instead of in plasma. The dyes commonly used for estimating plasma volume all show definite changes in their spectral absorption when either salt or protein (plasma) is added to the water solution. As a rule, these dyes have a greater color intensity in water than in plasma, and therefore if the dye plasma is read against a water standard, the calculated dye concentration will be too low and the plasma volume correspondingly too high.[44]

By using a spectrophotometer these difficulties can be readily overcome. With this instrument direct comparison of the unknown with a standard is eliminated. The dye con-

centration is measured in terms of optical density (the fraction of light absorbed by the solution at some particular wave length of light), which is directly proportional to the concentration of the dye; and absorption by the solvent itself is cancelled by simply reading the unknown serum against the control. Consequently, with the spectrophotometer one can determine directly the increase in plasma-dye concentration resulting from a single dye injection, regardless of whether or not the plasma contains residual dye. Another important advantage of spectrophotometry is that errors from hemolysis can be eliminated by the simple expedient of using a blue dye which has its peak of absorption in the red end of the spectrum where the absorption by hemoglobin is relatively insignificant. For this reason, and because it disappears slowly from the plasma, the blue dye T-1824 is quite satisfactory.

The dye-dilution method is based on the assumption that the dye is distributed solely in the plasma, and that none of it is taken up by the red blood cells. Tests have shown that T-1824 fulfills the latter requirement.[54] Much of the work done with the dye method has also been based on the assumption that the dye is uniformly distributed in the circulation in from four to six minutes. Time-concentration curves obtained on human beings, dogs, and cats show that uniform distribution usually takes longer and may, in special instances, require thirty to forty minutes. Since appreciable quantities of dye may in the meantime escape from the blood stream, it is impossible to calculate the volume accurately from any one sample obtained after mixing is complete. A satisfactory solution is shown in Fig. 367. The "disappearance" portion of the time-concentration curve is projected back to the time when dye was injected. This gives the dye concentration which would be obtained if mixing were instantaneous, that is if mixing occurred before any dye had escaped from the blood stream. With this technique, the determination of volume is independent of the circulation rate.

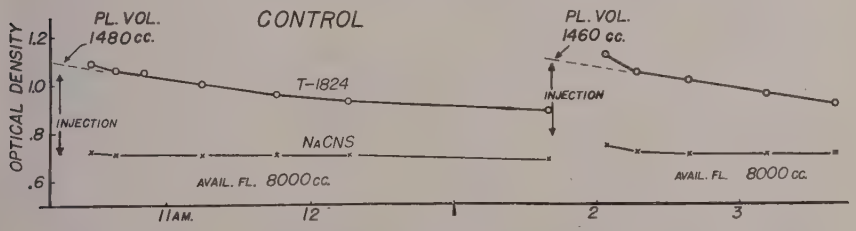


Fig. 367.—Time-concentration curves of the blue dye T-1824 and of sodium thiocyanate (see text).

During the period required for uniform distribution of the dye (twenty minutes or more) some escapes from the blood stream. By projecting the disappearance curve back to the time of injection one may correct for this loss and estimate the concentration of dye (expressed in terms of optical density) which would exist if uniform distribution occured immediately. The plasma volume is calculated from this value by the equation:

$$\text{Plasma volume in ml.} = \frac{\text{Conc. of standard dye sol. x ml. injected}}{\text{Conc. in plasma}}.$$

Sodium thiocyanate is usually eliminated so slowly from the body that the plasma concentration remains practically the same for several hours after uniform distribution has occurred. Therefore no correction need be made for disappearance, as in the case of T-1824. The volume of fluid available for dilution of thiocyanate is approximately equal to the volume of extracellular fluid (plasma plus interstitial fluid).[55]

It is incorrect to assume, as many have done, that the total blood volume can be calculated from the plasma volume and the hematocrit. Comparisons of total blood volumes as estimated, (1) from the dye method (which measures only the plasma volume) and the hematocrit, and, (2) from the carbon monoxide method (which measures the total volume of red cells in circulation) and hematocrit, show a discrepancy of 25-30 per cent.[127] Since the dye method gives the higher value, Smith, Arnold and Whipple[126] suggested that blood in the capillary bed is relatively richer in plasma than the blood in the large vessels. Direct observation on the flow of blood through smaller vessels has indeed revealed that this is the case. The cells move through these vessels in an axial stream which has a higher linear velocity than the surrounding zone of clear plasma. Fåhraeus[28] has demonstrated that the same phenomenon occurs in vitro with blood flowing through capillary tubes of small diameter (0.1 mm. or less), and maintains that it is a characteristic of all suspensions flowing through capillary tubes of small bore.

From the results of numerous investigations, it appears that the plasma volume per unit body weight is far from constant even within a selected group of normal individuals. Keith, Rowntree and Geraghty,[71] for example, found normal values between 42 and 56 ml. per kilogram body weight; and the writer, using the blue dye T-1824, has obtained results on normal medical students ranging from 37.6 to 58.5 ml. per kilogram. Similar variations have been reported by others, regardless of the method used. It is interesting to observe, in contrast to these findings, that repeated determinations on the *same* subject under similar conditions show a fairly constant plasma volume. There can be no doubt that individual differences of considerable magnitude actually exist. It is known that obese subjects have less plasma per kilogram body weight than normal persons, but there are undoubtedly a number of structural and physiological differences among individuals which play an important part. Changes with age appear only during the first two to three years of life. The volume in proportion to body weight is highest at six months, and then gradually falls until in the third or fourth year it is equal to the value for adults. Rowntree[113] has suggested that the blood and plasma volumes should be expressed in terms of body surface. Although the plasma volume does seem to be somewhat more closely related to body surface than to body weight, it is doubtful if much significance can be attached to single determinations unless they fall well outside the range of normal values.

For the purposes of the present discussion it is sufficient to bear in mind that the average plasma volume estimated from a large number of determinations is approximately 45 ml. per kilogram body weight. The vascular compartment of a man weighing 70 kilograms would therefore contain about 3,200 ml. of plasma, or, correcting for the plasma proteins, about 3,000 ml. of water (see Fig. 365).

The Interstitial Fluid Compartment.—The volume of the interstitial fluid is not subject to separate measurement, but it can be calculated by subtracting the volume of fluid in the vascular compartment from the total volume of extracellular fluid. The problem is, therefore, principally one of estimating the volume of the latter.

If there is no chloride in the intracellular compartment (and this seems to be the case at least in muscle), then the total extracellular fluid can be calculated from the concentrations of chloride in the serum and interstitial fluid and from the total chloride content of the body. In this manner Harrison, Darrow and Yannet[59, 104] have estimated that the extracellular water in the rabbit and the dog is equal to between 25 and 30 per cent of the body weight. Making the same calculations from sodium analyses the results are approximately 10 per cent higher. In either case the values are undoubtedly a little high since the distribution of electrolytes in muscle is probably not duplicated in certain glandular structures, the cells of which must, by the very nature of the secretions they produce, contain both sodium and chloride. Manery's[88] studies on the distribution in injected radioactive sodium and chloride indicate that in a number of tissues, particularly the brain, a considerable proportion of both sodium and chloride is intracellular; and furthermore, Amberson and his co-workers,[4] in their total plasmapheresis experiments with chloride-free perfusion fluid, found that chloride was retained by the stomach, spleen, salivary glands, and especially by the central nervous system.

A convenient and simple method of estimating changes in the volume of extracellular fluid in intact animals and in man was suggested by Crandall[19] on the basis of his studies of the bodily distribution of sodium thiocyanate. His results indicated that the fluid available for dilution of thiocyanate is approximately the same as the volume of extracellular fluid. This inference is supported by the observations of Lavietes, Bourdillon and Klinghoffer,[80]

that the substances sodium chloride, sucrose, and sulfate are also distributed through nearly the same volume of body fluid as sodium thiocyanate. The fact that neither sucrose nor sulfate enters the red blood cells is presumptive evidence that they also do not enter other cells in the body. Although thiocyanate enters the erythrocytes, its penetrability into other cells in the body seems to be no greater than that of sulfate or sucrose since, as we have said, all three yield the same values for "available fluid." It is excreted so slowly by the kidney that practically none of it is lost during the forty to fifty minutes required for uniform distribution. The plasma level is constant thereafter for several hours (see Fig. 367). Complete removal from the body takes from five to eight days.

It should be pointed out that the question which was raised in connection with the assumption that the extracellular fluid volume is equal to the total sodium or chloride space also applies to thiocyanate; namely, that this substance is secreted by various glands and therefore the fluid available for its solution probably includes some intracellular water. How important this is remains to be seen. After all, we have no absolute assurance that the extracellular space in the strict anatomical sense is identical with that which functions as such. Another characteristic of thiocyanate, which however would tend to give values for the "available fluid" volume which are lower than the true extracellular fluid, is that this substance is apparently not distributed in a 1:1 ratio between plasma and interstitial fluid. Lavietes[79] has observed that at equilibrium the concentration of thiocyanate is slightly higher in the plasma than in a perfusate because thiocyanate has an affinity for the plasma lipids. In this respect the more laborious bromide technique developed and employed by Brodie and his co-workers[14] is preferable to the thiocyanate method and, as one would expect, the estimated volume of extracellular fluid is somewhat higher. Furthermore, the experimental evidence shows that the bromide space agrees closely with the chloride space.

According to the results obtained with these techniques the extracellular fluid volume in man varies considerably from individual to individual, but the average is about 25 per cent of the body weight. Accepting this as a normal average and subtracting the volume of plasma (4.5 per cent of the body weight), we may conclude that the interstitial compartment is 18 to 20 per cent of the body weight. The volume of the interstitial fluid in a normal subject weighing 70 kilograms is therefore equal to about 14 liters. This value has been inserted in Fig. 365.

Intracellular Fluid Compartment.—Since we have no method for determining separately the volume of fluid in the intracellular phase, we can only calculate it from estimated values for the total body water and from the volume of extracellular fluid (plasma plus interstitial fluid). Assuming that the body is two-thirds water, the total water content of a normal subject weighing 70 kilograms is equal to 46 liters. Since the vascular and interstitial compartments together contain approximately 17 liters, we have 29 liters to be accounted for in the intracellular phase.

CHAPTER LXXIX

TOTAL WATER BALANCE; THIRST, DEHYDRATION AND WATER INTOXICATION

The total water content of the body is dependent upon the rate of exchange through the various channels shown in Fig. 365. Water is supplied in the form of fluid taken as such, but a surprising proportion also enters the body as an integral part of the food. Fruits and vegetables as a rule contain over 90 per cent water, and the so-called solid foods between 60 and 85 per cent. It is difficult indeed to find a constituent of the diet which contains less than 50 per cent water. When food is burned in the body, a certain amount of water is also liberated as the water of oxidation. An ordinary mixed diet yields about 300 ml. of water from this source; 100 grams each of fat, starch and protein yield, respectively, 107.1, 55.5 and 41.3 grams of water of oxidation.

Fluid taken by mouth does not become an integral part of the body until it has been absorbed from the lumen of the gut. This process, which occurs mainly in the small intestine, is preceded by the establishment of osmotic equilibrium between the fluid and the blood, and the rate at which absorption takes place is therefore determined somewhat by the concentration of the ingested fluid. In the case of hypertonic solutions, absorption is retarded by the initial diffusion of water from the blood. The rate at which the contents of the intestines pass into the blood stream also depends upon the diffusibility of the dissolved substances. Sodium chloride, for example, enters the blood with great rapidity, but magnesium sulfate, to which the wall of the intestine is practically impermeable, prevents absorption. This accounts for the purgative action of Epsom salts of which magnesium sulfate is the chief constituent.

Large quantities of fluid are secreted into the mouth, stomach and intestine in the course of digestion. Normally this fluid is not permanently lost from the body, but is reabsorbed as digestion proceeds. It has been estimated that the exchange is between 3 and 10 liters per day. Table CXVIII indicates the relative amounts which are secreted by the various digestive organs. With a turnover of this magnitude, greater than the plasma volume, it is not difficult to visualize the effect of continued loss of digestive secretions, such as occurs in persistent vomiting or diarrhea.

The amount of water normally lost through the kidneys is dependent upon many factors, chiefly upon the available supply of body water. Generally speaking, it bears an inverse relation to the amount vaporized through the skin and respiratory tract. Ordinarily, the renal and extrarenal channels discharge approximately equivalent amounts of water, about 1 liter each a day. In the tropics, urine secretion may be reduced to a minimum, while the greater part of the 10 or 12 liters of water drunk per day is lost through the skin. Under these conditions a considerable amount of sodium chloride is also excreted by the sweat glands, thus reducing the volume of water required by the kidneys for the excretion of salt. The normal variations in the urine output are indicated in Table CXVIII.

Since the quantity of water ingested is normally in excess of the bodily needs, the kidneys usually function as a spillway for the water not dissipated through the extrarenal channels; but when the water supply is meager, the kidney excretes salts and waste products in high concentration. Recent evidence indicates that the water output in the urine is regulated by the posterior pituitary gland. This question will be considered further in the chapter on urine secretion.

Except for a small amount of water excreted in the feces, extrarenal loss of fluid occurs through the lungs and skin. Loss through the lungs is determined by the ventilation and by the difference in vapor tension between the inspired and expired air. The expired air is not, however, saturated with water vapor as might be supposed. Direct measurement on alveolar air shows that even in the lungs the vapor tension is always somewhat lower (1.5 to 2.0 mm. of Hg) than the saturation point at the body temperature. In dogs, which are largely devoid of sweat glands, the evaporation of water from the mouth, lungs and respiratory passages can be increased by panting, an important means of dissipating heat. Panting is initiated mainly by a rise in the skin temperature but may also be facilitated by a conditioned reflex.

TABLE CXVIII

RATES OF TURN-OVER OF WATER BY VARIOUS ORGANS IN A 70-KILO HUMAN INDIVIDUAL, IN MILLILITERS PER 24 HOURS (From Adolph[2])

ORGANS	MINIMUM	LIBERAL
Salivary glands	500	1,500
Stomach	1,000	2,400
Intestinal wall	700	3,000
Pancreas	700	1,000
Liver (bile)	100	400
Lymph	700	1,500
Total recovered by body	3,700	9,800
Kidneys	600	2,000
Colon (feces)	50	200
Skin (insensible loss)	350	700
Sweat glands	50	4,000
Mammary glands	0	900
Total lost from body	1,050	7,800
Total turn-over	4,750	17,600

The loss of water through the skin is partly an insensible cutaneous loss and partly a visible secretion of sweat. The latter is negligible under basal conditions at ordinary room temperature but serves as an emergency mechanism to provide water for evaporation in case of need during exercise, exposure to high temperature and in fever. In extreme conditions the amount of sweat secreted may be very large (1 to 2 liters per hour in a hot bath).

As shown in Table CXVIII the insensible cutaneous loss is about 300 to 700 ml. per day. That the sweat glands contribute an insignificant part of this amount is indicated by the fact that a similar quantity of water is liberated from the skin of individuals who have no sweat glands. The volume of water lost as insensible perspiration bears a remarkably constant relationship to the metabolic rate.[25] Thus, conditions which increase the metabolic rate, such as exercise, the taking of food or hyperthyroidism, cause a proportional aug-

mentation of the insensible water loss. Dehydration and water drinking have no significant effect except when pushed to extremes. Serious disturbances of the body fluids do, however, influence the insensible perspiration, as do changes in skin temperature and changes in the blood flow through cutaneous areas.

We may then summarize the above discussion as follows: The respiratory and insensible cutaneous loss of water goes on continuously and at an approximately constant rate. The loss through the kidneys and sweat glands, however, fluctuates greatly. Conservation of water in time of need is effected principally through the reduction of excretion by the latter channels. Under normal circumstances the intake of water exceeds the requirements, causing the kidneys to excrete more water than is essential for the elimination of solids.

Regulation of the Water Intake: Thirst.—Although the water intake undergoes large variations in the course of natural existence, the water balance is maintained within surprisingly narrow limits, as indicated by the constancy of the body weight. In a subject studied for forty-nine days, Atwater and Benedict found that the water intake fluctuated from 880 to 2,440 ml. of water per day, the average consumption being 2,290 ml. per day. Under conditions of moderate work, the intake varied from 2,225 to 4,550 ml., an average for 66 days of 3,700 ml. per day. The report has been made by Hunt that in India a person may drink as much as 13 liters per day. These facts presuppose the existence of some mechanism for the regulation of the intake, adjusting it to the bodily needs. Dehydration is accompanied by a number of visible changes—dryness of the skin, shrinkage of subcutaneous tissue, decreased deformability of the skin and reduction in the urine flow. But these are of little concern to the dehydrated individual in comparison with the dry mouth and sensation of thirst which claim all his attention. This sensation is the warning signal indicating the need for increasing the water content of the body, and as such has great practical significance.

The question of the origin of the sensation of thirst has been a subject of controversy among physiologists for more than three-quarters of a century. One group has held that the sensation is of diffuse origin, since it is associated with conditions involving a general depletion of the body fluids and since it is abolished directly by intravenous injection of water or salt solution. Those who adhere to this point of view ascribe only slight significance to the local sensation of dryness in the mouth. According to Schiff, dryness of the mouth is merely a secondary phenomenon which . . . "bears no deeper relation to the general sensation than heaviness of the eyelids bears to the general sensation of sleep." The interpretation of various experiments brought forth in support of the theory that thirst is of diffuse origin does not withstand critical examination. Furthermore, the theory leaves one in a quandary as to how the sensation arises. Does it entail the existence of a special system of nerves which are sensitive to changes in the water content of the tissues and which serve to inform the central nervous system of these changes? There is no anatomical basis whatsoever for such an assumption. One might possibly claim that there is a center in the brain sensitive to increases in the concentration of the blood, but the difficulty with this explanation is that thirst is produced in the absence of increased concentration of the blood when the water content of the body is depleted by hemorrhage. There is now a large body of evidence which indicates that the sensation of

thirst is really what it seems to be; namely, a dryness of the mouth and throat. For a discussion of the older literature, the reader is referred to the review by Cannon.[17]

The theory that thirst is of local origin has been championed by Cannon, who in support of his view has drawn liberally upon the testimony of individuals who have suffered extreme thirst. It is a matter of common experience, for example, that thirst may be temporarily relieved by measures which merely serve to moisten the mouth and which do not alter the amount of water in the body itself. McGee,[95] a geologist of wide experience in the southwestern deserts of the United States, reports, "commonly the condition is alleviated by a moderate quantity of water; sometimes fruit acids and other acid substances, exciting a flow of saliva are requisite for relief; and in the practical life of the range, a pebble or nail carried in the mouth is often efficacious. . . ." Anyone who has experienced severe thirst is acutely impressed with the fact that the thirsty man's chief concern is to be relieved of the torment of dryness in his mouth and respiratory tract. That thirst is a local phenomenon is also shown by the fact that "breathing hot air free from moisture, prolonged speaking or singing, the repeated chewing of desiccated food, the inhibitory influence of fear and anxiety on salivary secretions, have all been observed to result in dryness of the buccal and pharyngeal mucous membrane, and in attendant thirst."[17]

The correlation between thirst and a reduced salivary flow was demonstrated by Cannon and has since been confirmed by others. In man, the salivary flow may be tested by measuring the amount of saliva secreted in response to chewing a tasteless gum at a uniform rate, or by breathing through the mouth. In a dog, the duct from one of the submaxillary glands may be exteriorized and the saliva collected in a funnel attached over the fistula. A uniform stimulus is provided by exposing the dog to a warm atmosphere, under which conditions the animal pants at a constant rate; as the mouth becomes dry, the salivary glands are reflexly stimulated to secrete.[45]

If Cannon's theory of thirst is correct, it should be possible to demonstrate that the elimination of the salivary flow, either by tying the salivary ducts or by complete extirpation of the salivary glands, causes thirst and stimulates drinking of water in spite of the absence of bodily dehydration. Montgomery[99] put this question to an experimental test by measuring the daily water intake of dogs before and after extirpation of the submaxillary, sublingual, parotid and infraorbital glands. Contrary to expectation, she found that the animals consumed no more water after the removal of the glands than they did before. It must be remembered, however, that the buccal mucosa is dotted with glands which are capable of secreting a certain amount of fluid. Miss Montgomery collected 8.9 grams per hour from this source in one of her dogs. To make the experiment crucial, the water intake should be tested under experimental conditions which cause drying of the buccal mucosa. This can be accomplished by exposing the animals to an atmosphere warm enough to make them pant. Gregersen and Cannon[48] demonstrated that under these conditions, dogs drank more than twice as much water after tying of the parotid duct and removal of the submaxillary, sublingual and intraorbital glands.

Further evidence of the relation between decreased salivary flow and the appearance of thirst is provided by a study of drinking habits in dogs.[47] Continuous records obtained under normal laboratory conditions show that dogs

rarely drink except when they are fed (Fig. 368); when food is withheld, they drink only about one-fourth of the usual amount. The need for water after meals is explained by the temporary withdrawal of body fluids for the formation of digestive juices. Since these secretions are reabsorbed in the later stages of digestion, the desire for water should also disappear. That this is the case may be shown by withholding water for six or eight hours after a meal and then measuring the water drunk, at which time the dog consumes much less water than it usually drinks during the postprandial period when given water *ad libitum*. The temporary dehydration after meals is reflected also in a marked fall in the salivary flow, a change which has been shown by the writer to occur in both man and the dog. These facts again demonstrate the intimate relation which exists between the state of hydration of the body and the salivary flow.

Since dehydration reduces the quantity of secretion produced all along the digestive tract, the observations which have just been described suggest that an abundant supply of digestive juices would be facilitated by the ingestion of generous quantities of water with meals. Water which is taken with food escapes quickly into the small intestine where it is promptly absorbed, while the food material remains in the stomach. That the water ingested

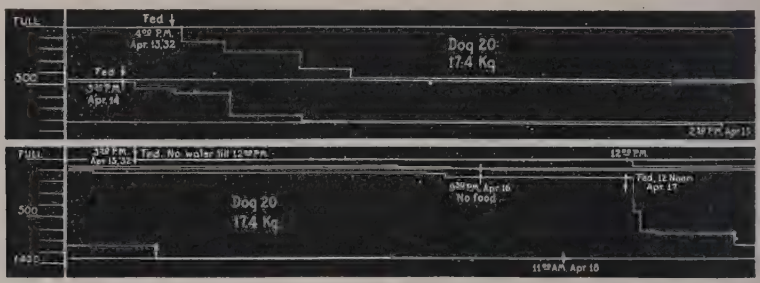


Fig. 368.—Drinking records on a dog. The length of the record covers a period of twelve hours. The upper chart covers a normal control period; it shows that most of the water drunk during twenty-four hours is taken within a few hours after the dog is fed. This is true no matter what time of day food is given. The lower record demonstrates that the postprandial thirst is temporary. On April 15 food was given at 3:30 P.M., but water was withheld until 12:00 midnight. At that time the dog drank only a small amount and consumed scarcely 100 ml. during the next thirty-six hours. The subsequent feeding on April 17 was followed by the usual ingestion of fluid. (From Gregersen.[47])

does not retard the rate of digestion was shown by Hawk and his collaborators.[96] He found that the ingestion of a liter of water, coffee or tea had no effect upon the rate of development of gastric acidity after meals. If cream is added to the tea or coffee, or if chocolate in equivalent quantities is taken, the rate of digestion is definitely retarded. This is in harmony with the observation that fatty foods leave the stomach much less quickly than do carbohydrates or proteins. It therefore seems that the only deleterious effect of taking water with meals is caused by the tendency to swallow food without adequately chewing it; the drinking of water after the food has been swallowed can be looked upon as beneficial in the sense that it provides a larger store of fluid in the body for the formation of digestive juices.

Granted that the immediate cause of thirst is a dryness of the mouth and throat resulting from a diminished output of saliva, it still remains to be shown how this secretion is reduced by dehydration. Under ordinary circumstances, the activity of the salivary glands is entirely determined by stimuli carried to them through the sympathetic and parasympathetic nerves. If these nerves are

cut, secretion ceases.* This suggests the possibility that in dehydration the reflex arc is either interrupted or partially blocked. But according to Morgulis,[100] this is not the case. He states, "In fasting dogs, even in an advanced stage of inanition, the submaxillary gland can be excited to activity through chorda tympani stimulation, the latent period being even shorter than in the normal dog. The saliva thus obtained, though less in amount than normally, showed no qualitative differences. The mechanism of reflex secretion is likewise apparently intact, since an augmented secretion of a clear and watery saliva is called forth by introducing acetic acid into the buccal cavity." Furthermore, he finds that, "The chorda tympani secretory fibers supplying the submaxillary gland retain their excitability to the very last moment of the animal's existence; stimulation

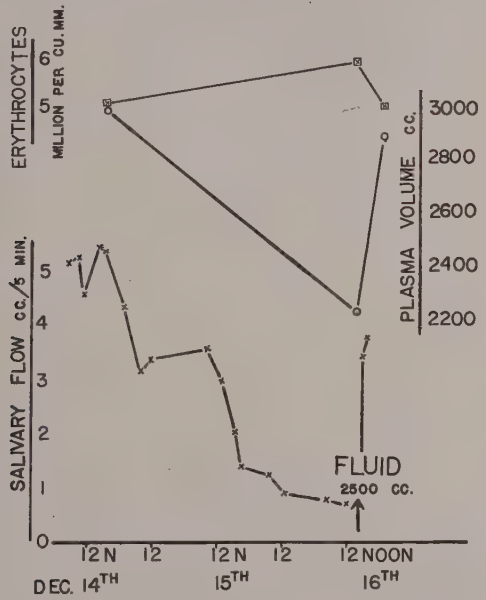


Fig. 369.—Changes in plasma volume and salivary flow produced by two days' water deprivation and the subsequent ingestion at one time of 2500 c.c. (ml.) of fluid. The salivary flow represents the amount of saliva secreted in response to breathing through the mouth for five minutes. The plasma volume was determined by the Keith-Rowntree method, observing the necessary precaution of reading the unknown against a standard of nearly the same strength. The body weight at the start was 85.6 kg. It dropped to 83.0 kg. after two days without food or water, but with the ingestion of 2500 c.c. (ml.) of fluid (water and ginger ale) it was again restored to normal. (Constructed from the data of Gregersen and Bullock: Am. J. Physiol. 105: 39, 1933.)

of the cervical sympathetic fibers, on the other hand, fails to provoke any secretion." We cannot, therefore, explain the reduction in salivary flow during dehydration on the basis of changes in the reflex arc or in the strength of the stimulus applied to the glands.

The influences which affect the salivary flow must operate through the blood stream. Since dehydration is normally associated with a concentration

*During degeneration of the nerves there is a small continuous flow of saliva known as the "paralytic secretion."

of the blood, it is well to consider the effect which this may have on the activity of the salivary glands. A characteristic of all true secretory cells is that their activity is independent of the composition and the pressure of the blood flowing through them. Likewise, the quality of the secretion which they produce is not, as a rule, conspicuously altered by changes in the composition of the blood. This can be demonstrated for the submaxillary gland by continuous injections of various substances directly into the external carotid artery, from which the gland receives its blood supply (unpublished observations by the writer). A further point is that the activity of the submaxillary gland results in the withdrawal of a very large proportion of the fluid from the blood passing through it. During active secretion induced by stimulating the chorda tympani, for example, the blood flow through the submaxillary gland of a cat or dog is about 5 to 6 ml. per minute per gram of gland,[6] while the secretion rate may be 1 to 2 ml. per minute per gram of gland. Since only one-half of the blood is plasma, the secretory cells must have extracted between one-third and one-half of the

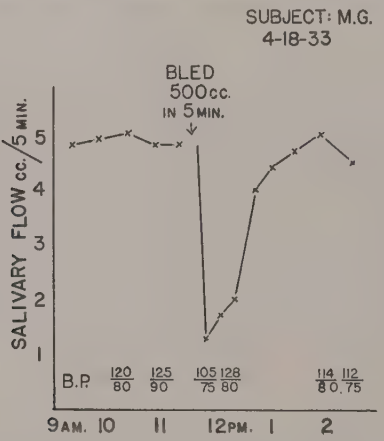


Fig. 370.—Curve showing the reduction in salivary flow caused by the sudden withdrawal of about 10 per cent of the blood from a normal subject. The salivary flow was measured by the response to breathing through the mouth.

total quantity of water in the blood which passes through the gland. A small amount of fluid is also drained off as lymph. These cells are thus capable of withdrawing fluid from the blood when the latter is far more concentrated than it is in dehydration. Consequently, it is highly improbable that the relatively small hemoconcentration brought about by a moderate loss of body water is a direct factor in causing a diminished secretion of saliva. The possibility becomes even more remote when we recollect that hemorrhage, which if anything dilutes the blood, also lowers the salivary flow (see Fig. 370).

Since the glands secrete large volumes of fluid in proportion to their own weight, their activity must depend intimately upon the blood supply. If the carotid artery is partially occluded while the submaxillary gland is being stimulated through the chorda tympani, there is a prompt fall in the secretion rate. Gesell[11] has shown that the increase in blood flow through this gland during activity is directly proportional to the volume of saliva produced. He has also

demonstrated[40] that the blood flow through the resting gland may be reduced to one-seventh of its original value by a hemorrhage amounting to only 10 per cent of the total blood volume, in spite of the fact that the blood pressure may be unaffected by the hemorrhage. The compensatory vasoconstriction which accompanies a decrease in blood volume apparently restricts the blood supply to the salivary glands as well as to other areas in the body supplied with vasoconstrictor nerves. This gives us a sensible explanation for the reduced salivary flow in dehydration, provided it can be shown that salivary secretion and blood volume undergo parallel changes in dehydration and in other general conditions which are conducive to thirst.

Concurrent changes in salivary flow and plasma volume may be seen after water deprivation, after ingestion of a large meal taken without water, after profuse sweating in a hot bath and when the body water has been depleted by the diuresis incident to the intravenous injection of concentrated (50 per cent) sucrose solution (16-18 grams per kg. body weight). Fig. 369 shows the observations made on a human subject during two days without water. The correlation in this and other experiments between salivary flow and plasma volume is strongly indicative of the dependence of thirst upon a reduction in the fluid volume of the blood. This is particularly well illustrated in an experiment with hemorrhage (Fig. 370). The subject was bled 500 ml. in five minutes from the right antecubital vein. There was only a small and temporary fall in the blood pressure, indicating the presence of an effective compensatory vasoconstrictor mechanism, but the salivary flow immediately fell to one-fifth of its previous level and did not return to normal for over an hour, presumably the time required for restoration of the fluid volume of the blood. Similar results have been obtained on dogs. Putting all the above facts together, we arrive at the conclusion that the decrease in plasma volume caused by depletion of the water content of the body is significant as the first step in the physiological mechanism of thirst which signals the need for an increase in the water intake. A dry mouth is therefore an important physical sign of a lowered blood volume, a fact which the surgeon has inferred from his practical experience; namely, that a patient with a dry mouth is a poor surgical risk and cannot withstand hemorrhage as well as the patient whose tongue is moist and glistening.

Although this interpretation offers a reasonable account of how the intake is adjusted to meet the water deficit in simple dehydration (loss of water alone), one cannot leave the question without considering a number of unexplained observations which indicate that there may be other physiological changes besides those described above, perhaps involving mechanisms as yet unknown, which also determine the presence or absence of the local sensation of thirst or the subjective impression thereof. For one, the accuracy with which the dog, for example, estimates a water deficit is rather surprising. The dehydrated animal will ingest an amount of water closely approximating the deficit in a few minutes, sometimes drinking without interruption and then stopping abruptly, apparently satisfied.[1] How does the animal judge his needs so closely? It is obvious that enough water to relieve the dehydration could not be absorbed in such a short period of time. From his studies on sham drinking in dogs with esophageal fistulas, Bellows[9] concludes that there are at least two processes involved. He states that: "Passage of an excessive amount of water through the mouth and pharynx confers immediate but tem-

porary satisfaction of thirst. The repetitive act of drinking and swallowing water is inhibited when the ingested water deficit enters the gut below the upper esophagus. The short period of temporary satisfaction secured by the passage of water through the mouth and pharynx is superseded by the delayed process of permanent satisfaction operating lower in the gut." The presence of water in the gut does not immediately inhibit drinking. If the estimated deficit is administered through a gastric fistula the animal will, if permitted, nevertheless promptly drink as much as he would have ingested without water in the stomach. If, on the other hand, water is withheld for ten to fifteen minutes the dog has lost his desire to drink.

For many years it has been known that the intravenous injection of hypertonic salt solution gives rise to thirst. On the basis of this fact a number of investigators have favored the view that the water intake is regulated according to the concentration of electrolytes in the body fluids. It is quite true that the serum electrolyte concentration tends to increase in severe dehydration, but it should also be noted that when the dehydrated dog is given water *ad libitum,* the electrolyte concentration in the blood frequently drops considerably below the initial normal level. In other words, according to this criterion he takes more water than is required to restore his body fluids to the normal state. That the answer is not as simple as one might suppose is further demonstrated by a detailed study on dogs of the drinking in response to salt.[68] In any one animal the amount of water ingested under standard conditions is directly and quite accurately proportional to the quantity of sodium chloride injected. Nevertheless one animal may regularly drink twice as much as another after the same dose. And again we must emphasize that the dog completes his drinking in a few minutes; that is, before the ingested water could effectively reduce the electrolyte concentration in the body fluids. Moreover, hypertonic solutions of the non-electrolytes sucrose, sorbitol, and to less extent glucose, are also effective in causing thirst. At any rate it should be noted that changes in salivary flow may constitute an important part of the thirst mechanism in these experiments. In man, the thirst caused by the injection of 300 ml. of 5 per cent sodium chloride (and the same is true when hypertonic sodium chloride is taken by mouth) is associated with an immediate reduction of the salivary flow to one-tenth or less of its normal value. If, however, the subject drinks 500-800 ml. of water about twenty minutes before the salt is given, the sensation of thirst is slight or entirely absent and the salivary flow remains essentially unchanged.

Gilman[42] has suggested that thirst might be determined specifically by dehydration of the intracellular compartment, a view favored also by Dill.[22] This would account for the thirst caused by salt and other substances which cannot penetrate the cell barrier, and, as Gilman noted, the absence of thirst immediately after the intravenous injection of urea to which the cell wall is freely permeable. As additional evidence Gilman cites the well-known fact that the experimental depletion of the extracellular electrolytes by intraperitoneal injection of isotonic glucose (Darrow and Yannet[21]), which results in a drastic decrease in both plasma and interstitial fluid volume as water moves into the intracellular compartment, is not associated with thirst. Dogs so treated will not drink water in spite of the fact that the mouth is exceedingly dry. This behavior may, however, be related to an impairment of the sensory

mechanism underlying the sensation of thirst, for McCance[94] reports that salt deficiency in man results in a loss of taste. Or speculating still further, it may be that an entirely different mechanism concerned with control of salt balance is taking precedence over the control of water balance. Clearly, the ingestion of water under these circumstances would merely serve to aggravate the already serious dilution of the electrolytes in the body fluids. One might add that the same disturbance in water balance (depletion of extracellular electrolytes and shift of water from extra- to intracellular compartment without altering the total body water) brought on gradually by sucrose diuresis and maintained by a salt-free diet, has been found to increase the daily water intake by three- to fourfold. (Unpublished observations by J. H. Holmes.) The evidence on the relation of intracellular hydration to thirst is therefore discouragingly contradictory at present.

Although several endocrine glands have, under special circumstances, been shown to affect the water intake, there is little indication that they play an essential role in or directly influence the thirst mechanism itself. For example, it has been noted that a subcutaneous injection of pitressin, administered twenty to thirty minutes prior to the injection of hypertonic salt, inhibits drinking for about ten minutes.[9] That the adrenal cortex may influence thirst is shown by the recent observation that large doses of desoxycorticosterone in normal dogs produce polydipsia.[106] Excessive doses of thyroid also increase the daily water intake.[75]

Dehydration.—The length of time during which life may be sustained without water differs greatly with the species.[89] Moths and serpents, for example, can live for very long periods with no water, and among the mammals the camel shows an extraordinary resistance to dehydration. Most animals, however, can exist without water for only a limited period, the length of which is modified by environmental conditions and bodily activity, and probably also by the differing capacity of individuals of the same species to withstand dehydration. Man has been known to survive eighteen days under average conditions of temperature and humidity, but under extremes of heat and exposure to the sun death may occur in two or three days. McGee[95] reports the remarkable case of a Mexican lost in the desert who walked and crawled 150 miles during a period of seven days and managed to sustain life by drinking his own secretions. Under ordinary laboratory conditions, dogs succumb to water deprivation in from two to eight weeks, and rabbits in about fourteen days.

Dehydration is frequently an important clinical problem. In the diarrheas of infancy and in Asiatic cholera, large quantities of water may be lost in the stools. Vomiting, and in particular the vomiting associated with pyloric obstruction, depletes the supply of body water so rapidly that 20 per cent of the body weight may be lost in one or two days.

Some of the tissues are more dependent than others upon their water supply in order to function. It is said that muscles, for example, may lose from 10 to 20 per cent of their total water without impairment of function, as determined by electrical records of activity of muscles after removal from the body. The skin can lose an even larger proportion of its water without permanent damage to itself or to the organism. Marriott has emphasized that this is not true for the blood, and that death from dehydration is caused by an increased viscosity of the blood. The circulation through the tissues is impaired and the blood tends to stagnate in the capillaries; in extreme dehydration the blood becomes so viscous that there may be no bleeding from deep cuts.

Water Intoxication.—Harmful effects from the ingestion of large quantities of water are not usually observed if the kidney is normal. In patients with impaired renal function, however, the administration of large doses of water may produce headache, dizziness, vomiting and cramps, together with a marked increase in weight and an increase in the blood pressure. This condition, which is known as "*water intoxication,*"[112] can be readily produced in dogs by giving water by stomach tube, in combination with injections of posterior pituitary extract. Since the latter inhibits the excretion of water but does not interfere with its absorption from the gastrointestinal tract, the animals become overloaded with water. Water intoxication in dogs is characterized by asthenia, restlessness, diarrhea, nausea, retching, vomiting, tremor; salivation, muscle twitching, ataxia, convulsions (from increased intracranial pressure) and stupor or coma. If the forcing of water is continued, death ensues. The symptoms can be rapidly relieved by injecting hypertonic salt solution or by giving urea, both of which overcome the effect of the pituitary extract and produce diuresis and withdrawal of water from the tissues.

The disturbances in bodily function associated with water intoxication are presumably caused by a dilution of the body fluids with respect to salts. A similar situation is encountered in heat cramps. Men who work in boiler rooms, steel foundries and other places where they are continually exposed to high temperature, lose large quantities of salt in the sweat. If under these conditions the water content of the body is restored only with water, the concentration of salt in the body fluids decreases to a point where the normal functions are disturbed. Although in this case the water content of the body is not increased above normal, the symptoms which appear are similar to those produced by water intoxication. Heat cramps can be avoided by drinking a solution of sodium chloride instead of water. It is said that this solution, which ordinarily is quite distasteful, is taken with great satisfaction under conditions conducive to excessive sweating.

The dependence of the total water content of the body upon the retention of salts has already been noted and may be illustrated in a number of other ways. For example, the dehydration which accompanies experimental pyloric obstruction in dogs cannot be alleviated by water alone. With the continued secretion of gastric juice, the animal loses considerable quantities of chloride and some sodium. The preponderance of base left in the blood is excreted by the kidneys with the result that both the sodium and chloride in the extracellular fluids are rapidly depleted. Under these circumstances water has no therapeutic value and is merely excreted. The same end result may be produced in a dog by allowing the pancreatic juice to be drained from the body through a fistula.[38] Since this secretion consists mainly of sodium bicarbonate, the body is left with a relative excess of chloride which is eliminated by the kidney. In this case also the progressive dehydration is not prevented by allowing the dog water *ad libitum;* nor is it alleviated by feeding meat, in which the fixed base is almost entirely potassium. This base, which cannot take the place of sodium in the extracellular fluids, is merely excreted. Another illustration is the gradual loss of body fluid which occurs in individuals living on salt-free diets.[94] Also it is a matter of common clinical observation that in patients whose renal mechanism for the excretion of salts is impaired, the addition of salt to the diet causes retention of fluid; and further, that the

problem of removal of edema fluid is in reality a problem of bringing about the excretion of sodium chloride. The storage of water goes hand in hand with the storage of salt; the one cannot be retained for any considerable length of time without the other. Hence, either one given alone usually acts as a diuretic.

The Influence of the Central Nervous System and Hormones Upon Water Exchange.—Among the oldest observations which indicate a dependence of the total water exchange upon the central nervous system, is the finding of Claude Bernard that a puncture in the floor of the fourth ventricle causes an increase in the urine flow. Further evidence that the central nervous system may affect the total water exchange is the common association of diuresis with nervous excitement.

Brain tumors in the region of the pituitary gland are sometimes associated with an extraordinary polyuria and an insatiable thirst, a disease known as diabetes insipidus. Cases have been reported in which 35 to 40 liters of urine were secreted daily. Since the administration of a small amount of pituitrin (posterior lobe extract) ordinarily restrains the abnormal elimination,*[138] the belief has grown up that the disturbance is the result of hypofunction of the posterior lobe of the pituitary. Ranson and his co-workers[35] have shown that the functional integrity of the posterior lobe is dependent upon its nervous connections with the nucleus supraopticus. In cats, bilateral destruction of this nucleus results in polyuria and atrophy of the posterior lobe. There has been considerable disagreement among observers as to the original cause of the increased water output, that is, whether it is due initially to an abnormal thirst or to an increase in the elimination of water by the kidneys. That the thirst mechanism in this disease is functioning abnormally seems to be indicated by reports that the desire for water cannot be abolished by desensitizing the buccal mucosa with local anesthetics. This contention that the thirst mechanism is abnormal is not supported by some recent observations which showed that the thirst in a severe case (urine output 18-20 liters per day) could be completely relieved by merely increasing the water intake sufficiently to maintain the normal plasma volume and body weight.[51] Under these conditions the salivary flow also rose to a normal level. Furthermore, when relief from thirst was obtained by giving pituitrin, the plasma volume increased. Indeed this patient showed the same parallel changes in plasma volume and salivary flow as a normal subject.

Other glands of internal secretion have important though as yet little understood effects on the total and internal fluid exchange. The adrenal cortex, for example, seems to be concerned in regulating the excretion of electrolytes and in maintaining the normal distribution of fluid between the extra- and intracellular compartments.[60, 83] Some investigators ascribe specific diuretic effects to the anterior pituitary gland and the thyroid, but these effects may be simply the result of changes in the metabolic rate. The periodic retention of fluid during the oestrus cycle in lower animals and the premenstrual edema in women are further indicative of the existence of complex relations between the water balance and the internal secretions.

*The effect of pituitrin on the kidney will be considered in the following section (Part IX).

CHAPTER LXXX

INTERNAL FLUID BALANCE

Translocations of water in the organism can only to a certain extent be explained by known physical and chemical forces. In many instances the living membrane participates actively in the fluid exchange, causing water and solutes to move in a direction opposite to the concentration gradients. Where this so-called vital process does not participate, the movement of fluid is largely determined by osmotic and hydrostatic pressures. Chemical hydration and electrical potentials are also known to affect the exchange of water within the organism, but it is difficult at present to evaluate their significance quantitatively.

As we have seen above, the membranes which separate the vascular from the interstitial compartments and those which separate the latter from the intracellular compartment have peculiarities of permeability which maintain an unequal distribution of solutes in the three compartments. The barrier between plasma and tissue fluid permits the passage of all constituents in the plasma, with the exception of the proteins. The barrier between the extra- and intracellular fluids is not only impermeable to proteins but also normally prevents the passage of sodium, potassium, chloride and a number of other constituents. Without these barriers, which are permeable to water but which discriminate against the dissolved substances, the force known as osmotic pressure would no longer exist.

Osmotic Pressure.—This is the result of an unequal distribution of water on two sides of a membrane. If an aqueous solution of sucrose is separated from pure water by a membrane which permits the free passage of the water but not of the sugar, water will move into the solution until the sugar theoretically attains infinite dilution. By raising the hydrostatic pressure of the solution, a point is finally reached at which the water molecules move out of the solution at the same rate as they enter. The pressure which is required to prevent addition of water to the solution is a measure of its osmotic pressure. It so happens that the osmotic pressure which is developed by the sugar in a system such as the above is equal to the pressure which the same number of molecules of a gas would exert if they were confined to the same volume as the sugar solution. From this one might be led to suppose that the sugar, or solute, in some mysterious way attracts water in an effort to enlarge the space in which it is confined. *Water moves across the membrane not because of some peculiar attraction of the sugar molecules for water but because the sugar displaces some of the water molecules and therefore the concentration of water is less inside than outside.* Hence, water moves into the solution until the diffusion pressure of water is the same on both sides of the membrane. Since the diffusion pressure is dependent not only on concentration but also on the hydrostatic pressure, the movement of water into the solution ceases when the hydrostatic pressure there has risen to a point which counterbalances the effect of unequal concentration of water on the two sides of the membrane. If we now substitute for sugar some substance, let us say sodium chloride, to which the membrane is permeable but which, nevertheless, diffuses through it more slowly than the water, the difference in concentration of water on the two sides of the membrane will be maintained only temporarily, and the osmosis will therefore be cor-

respondingly temporary. In the body we have situations analogous to both of the cases just described. Long ago Starling[133] pointed out that the plasma proteins exert a continuous osmotic pressure because the capillary wall is practically impermeable to them. The crystalloids which pass through it with ease exert no osmotic pressure unless their distribution is altered suddenly, and then their effect on movement of water is only transient. Therefore, the effective osmotic pressure of the plasma is usually dependent solely upon the plasma proteins. In general their osmotic pressure is balanced by the hydrostatic pressure in the capillaries. However, the tissue fluid immediately adjacent to the blood capillaries contains a small amount of protein, enough to reduce the effective osmotic pressure of the plasma. The tissue fluid is also under a certain amount of hydrostatic pressure (the latter being influenced by the degree to which the tissue spaces and cells are distended with fluid) which reduces the filtration pressure in the capillaries.

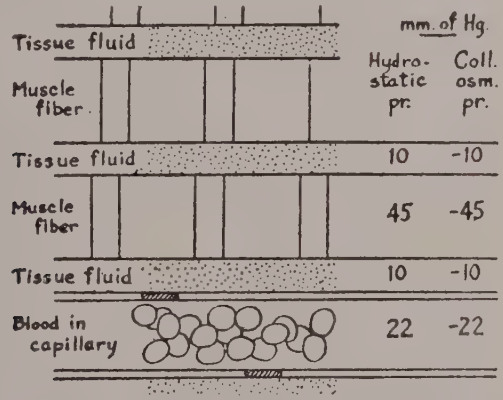


Fig. 371.—Diagram representing the balance of forces concerned in the osmotically steady state in average mammalian muscle tissues. It should be emphasized that the values for hydrostatic and turgor pressures are hypothetical because it is not known whether the colloid osmotic pressure of muscle measures the force effective in controlling the movement of water. (From Adolph.[2])

The osmotic and hydrostatic pressure relationships between blood and tissue and between tissue fluid and cells are shown in the accompanying diagram (Fig. 371). It shows that the equilibrium is determined mainly by four factors: "... the blood's hydrostatic pressure within the exchanging vessels, the turgor pressure and deformational tension of the tissue around the capillaries, the effective osmotic pressure of the blood plasma, and the effective osmotic pressure of the tissue cells."[72] With the exception of intracellular hydrostatic pressure, these forces have all been measured. Since the limiting membranes are not rigid, it is apparent that the hydrostatic pressure and the effective osmotic pressure must balance in each compartment.* Great flexibility in the movement

*The notion that a considerable portion of the water in the body is *"bound"* has not been supported by recent experimental evidence. Hill, using measurements of vapor pressure as the test for free water, estimates that the amount of bound water in the blood is less than 2 per cent of the total. In mammalian muscle it has been found that at least 94 per cent of the total water is capable of diluting electrolytes. Ultrafiltration experiments on blood serum, gelatine, glycogen, casein and starch show little evidence of bound water in these substances. Practically all the water in the body is free in the sense that it is available for dissolving substances and for taking part in fluid exchange.[77]

of fluid in such a system may be achieved by the body through changes in capillary pressure and permeability. When and to what extent changes occur in the intrinsic permeability of the capillary wall is difficult to determine.[77] In general it seems to be enhanced by capillary dilatation, but since the latter is also as a rule accompanied by increased capillary pressure, the relative importance of the two factors in furthering filtration cannot be estimated readily. Since vascular adjustments may be attended by alterations in capillary pressure and caliber, it is clear that the vasomotor system is a prime factor in preventing or promoting the local and general movement of fluid between blood and tissues. Through its integrative action the vasomotor center may permit fluid to be filtered in one part of the circulation and absorbed in another without significant disturbances in the total volume of the plasma. Likewise it compensates for exchange of fluid between the plasma and the external environment.

Evidence of the movement of water between blood and tissues can sometimes be obtained from changes in concentration of hemoglobin or plasma protein. The deduction from such measurements, however, is based on the assumption, frequently erroneous, that the total amount of plasma protein or the number of red cells in circulation remains constant (see Table CXVI). This method has the further disadvantage that it yields no information about the absolute amount of fluid exchanged, a matter of the greatest importance. A dependable method for estimating the absolute changes in plasma volume is essential for a complete investigation of the physiological conditions which determine the balance of fluid between blood and tissues. At present the most satisfactory way of measuring rapid changes in the plasma volume is to follow the changes in concentration of a slowly diffusible dye injected intravenously in a measured amount, the method described in Chapter LXXVIII.

Gravity.—The effect of capillary pressure on the exchange of fluid between blood and tissues is illustrated by quiet standing. That the increased venous pressure in the lower extremities under these circumstances results in a loss of fluid from the circulation is shown by the rise in plasma protein concentration and by the increase in the volume of the legs. If the subject then reclines, the fluid is soon restored to the circulation. Moving about will, to some extent, produce the same result by relieving the venous congestion and facilitating the drainage of lymph from the legs. Landis and Gibbon[78] have demonstrated that in experimental venous congestion filtration is at first rapid, but that at the end of about thirty minutes there is no further change because the tissue fluid pressure has risen to a point where it counterbalances the capillary pressure. A critical discussion of the various factors involved may be found in the review by Landis.[77]

Muscular Exercise.—Marked changes in the distribution of water and electrolytes have been found to occur during muscular activity. It has been known for some time that activity of skeletal muscle causes an increase in its weight.[7] More recently Fenn and co-workers[29, 30] have shown that the muscle cells lose potassium and take up sodium, and there is an increase in the volume of extracellular fluid in the active tissue. In man, vigorous muscular exercise produces a rise in the concentration of the blood.[23] If a measured amount of a slowly disappearing dye (T-1824) is injected intravenously and its concentration in the plasma determined at frequent intervals (see Fig. 367), it is possible to obtain a fairly accurate estimate of the quantity of fluid which leaves the circulation during exercise and the rate at which this fluid is subsequently restored. In the experiment shown in Fig. 372, the subject lost 470 ml. of fluid from the

plasma in ninety seconds (a decrease of 16 per cent in the plasma volume), whereas complete restoration of this fluid to the circulation required about an hour. The plasma protein concentration and the per cent of red cells also reflect these changes.

Adrenalin and the Sympathetic Nervous System.—From the statements made earlier, one might expect that stimulation of the sympathetic system and the secretion of adrenalin would greatly alter the internal fluid balance, since they have a marked effect on the pressure and distribution of the blood. Indeed it has been reported that continuous intravenous injections of adrenalin and intense sympathetic discharge will cause hemoconcentration and reduce the volume of plasma to a degree which produces shock.[36] Observations made by the writer and two associates on unanesthetized dogs[53] and cats[58] in which the plasma volume changes were followed during continuous intravenous injections of adrenalin have not confirmed these reports. In unanesthetized dogs, the effect of adrenalin in this respect is apparently unpredictable. The plasma

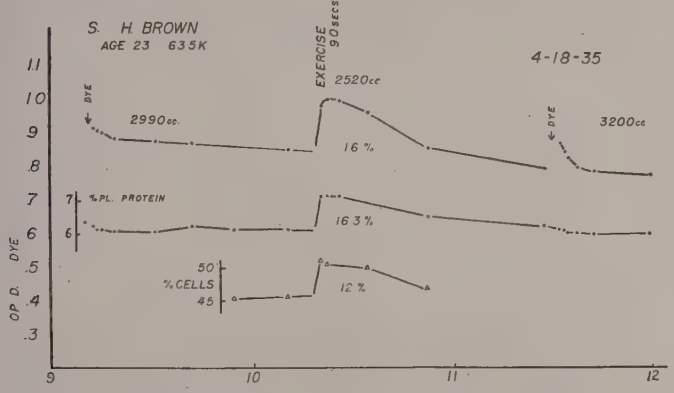


Fig. 372.—Showing that a short bout of vigorous exercise (running at top speed for ninety seconds on a treadmill) results in a marked decrease in plasma volume as measured by the plasma concentration of the dye (T-1824) injected at the start of the experiment. The change is also reflected by the rise in the plasma protein and erythrocyte content of the circulating blood. Full restoration of the plasma volume requires from thirty to sixty minutes. This experiment illustrates the rapidity with which fluid shifts between blood and tissues may occur. (Unpublished experiment by Gregersen, Dill and Meade.)

volume may rise, fall or remain unaltered; but in any case, the change with physiological doses is not great enough to impair the circulation. In cats, there is no significant change. Removal of the sympathetic system in this species produces as a rule a striking increase in the plasma volume, a result one would expect inasmuch as the blood pressure is still approximately normal in spite of the loss of vasomotor tone. In the dog the results have so far been conflicting.

The ultimate explanation of these and many other observations of a similar nature requires more information concerning the fundamental problem of control of capillary pressure, especially its relation to the vasomotor system. It is useful to recall that the capillary pressure is very sensitive to changes in venous pressure. Unfortunately, our knowledge of the vasomotor control of the veins is less complete than on the arterial side in which pressure changes

appear to take place without much effect on the capillary pressure. A clear illustration of the latter is the fact that in the unanesthetized dog the arterial pressure may be reflexly raised to the neighborhood of 200 mm. Hg for an hour by occluding both carotid arteries, without thereby producing any change in the plasma volume.[46]

Other Hormones.—Among the hormones which influence the distribution of fluid between blood and tissues is the vasopressor principle (pitressin) from the posterior lobe of the pituitary. When this substance is injected alone, there is no marked change in the concentration or the volume of the plasma; but if water is ingested at the same time, diuresis is delayed for from three to four hours and the water content of the blood is increased. Since hydremia does not result from the ingestion of a similar quantity of water alone, it would appear that pituitrin interferes with the removal of the absorbed water from the plasma. This explanation is supported by the observations that pituitrin retards the escape from the blood stream of a large variety of substances, either foreign or naturally occurring in the plasma. Whether the effect is caused by an intrinsic change in permeability of the capillary wall or is simply the result of changes in the capillary circulation is not known.

CHAPTER LXXXI

THE CEREBROSPINAL FLUID

The formation and absorption of cerebrospinal fluid constitute a problem of internal fluid exchange which is frequently a matter of practical concern. Treatment of hydrocephalus and of eclampsia in its acute states, not to mention the multitude of cranial injuries that result from automobile accidents, requires a clear understanding of the factors which determine the movement of water between blood and the cerebrospinal fluid.

Under normal conditions, the cerebrospinal fluid is a clear, limpid liquid, devoid of protein and containing very few cells (4-6 per cubic mm.). It fills the ventricles of the brain and the subarachnoid space of the cerebrospinal axis, from which it may be collected by a lumbar or cisternal puncture. Its total volume in man has been variously estimated at between 60 and 150 ml. However, if a needle is left in the cisterna magna, very much larger quantities than this can soon be collected, showing that the fluid is continually being renewed. It circulates from the lateral ventricles where it is secreted by the choroid plexuses, passes through the third ventricle, the aqueduct of Sylvius, to the fourth ventricle, from which it escapes into the subarachnoid space by way of the foramina of Magendie and Luschka, and is eventually absorbed through the arachnoidal villi into the venous sinuses.[145] A small amount of fluid is also added to the subarachnoid space from the perivascular spaces of the brain.

That the cerebrospinal fluid is secreted by the choroid plexus was demonstrated in a striking manner by Dandy. He showed that the internal hydrocephalus which develops after obstructing one foramen of Munro is prevented by extirpating the choroid plexus on the same side. Absorption of the cerebrospinal fluid into the venous sinuses was demonstrated by Weed, who, by injecting Prussian blue reagents into the subarachnoid space and subsequently fixing the brain in an acid medium to precipitate them, found that the granules had passed into the venous sinus through the arachnoid villi. Except for a small absorption through the lymphatic vessels by way of the perineural spaces, the foreign solution did not pass through membranes in any other portion of the subarachnoid space.

So strong is the similarity between the composition of cerebrospinal fluid and an ultrafiltrate of serum that a number of observers have been led to ascribe the production of cerebrospinal fluid to a purely physical process. That osmotic equilibrium exists between spinal fluid and serum is shown by the identity of the freezing points of these two fluids. Moreover, the difference in chloride concentration of spinal fluid and serum is in accord with the Gibbs-Donnan equilibrium. But beyond this point, according to Peters,[104] the evidence fails to substantiate the theory that spinal fluid is a true ultrafiltrate of serum. Glucose, nonprotein nitrogen and urea do not appear in the concentrations to be expected if true equilibrium existed between the two fluids. The distributions of bicarbonate, calcium phosphate and total base likewise show a discrepancy which is

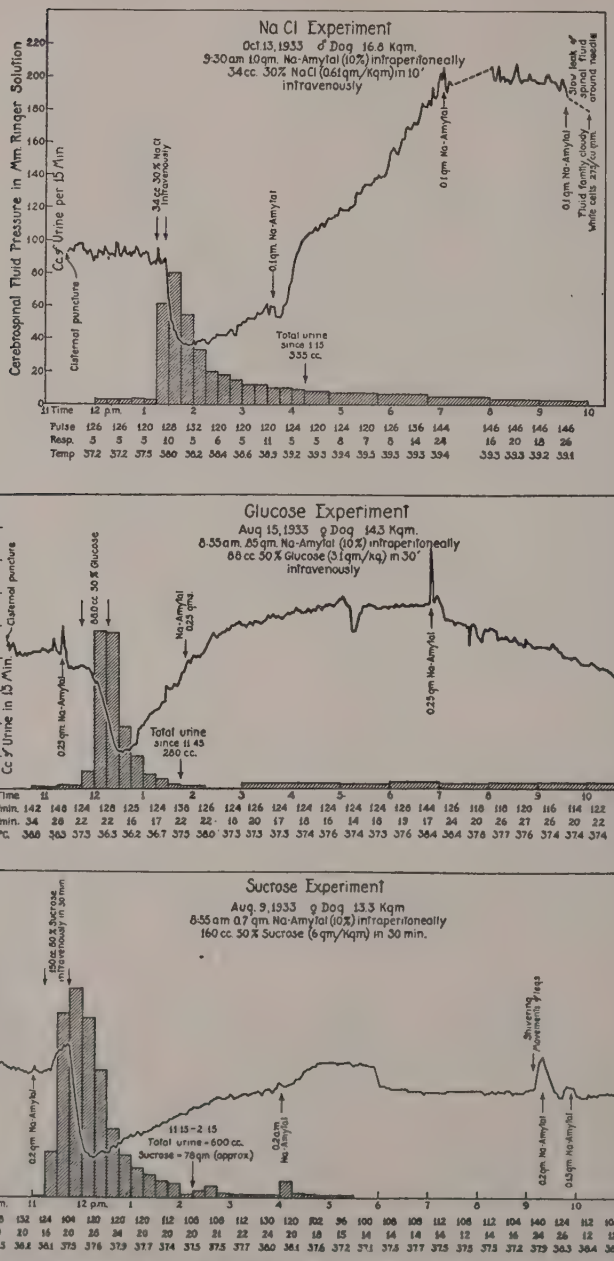

Na Cl Experiment
Oct 13, 1933 ♂ Dog 16.8 Kgm.
9:30 am 10 gm. Na-Amytal (10%) intraperitoneally
34 cc. 30% NaCl (0.61 gm./Kgm.) in 10' intravenously
Cerebrospinal Fluid Pressure in Mm. Ringer Solution
Cc. Urine per 15 Min.
Cisternal puncture
34 cc. 30% NaCl intravenously
0.1 gm. Na-Amytal
0.1 gm. Na-Amytal
Total urine since 1 15 335 cc.
0.1 gm. Na-Amytal
Fluid faintly cloudy White cells 27/cu mm.
Slow flow of fluid around needle
Time 12 p.m. 1 2 3 4 5 6 7 8 9 10
Pulse 126 126 120 128 132 120 120 120 124 120 124 120 126 136 144 146 146 146 146
Resp. 5 5 5 10 5 6 5 11 5 5 8 7 8 14 24 16 20 18 26
Temp 37.2 37.2 37.5 38.0 38.2 38.4 38.6 38.3 39.2 39.3 39.4 39.3 39.3 39.3 39.4 39.3 39.3 39.2 39.1
Glucose Experiment
Aug 15, 1933 ♀ Dog 14.3 Kgm.
8:55 am .85 gm. Na-Amytal (10%) intraperitoneally
88 cc 50% Glucose (3.1 gm./kg.) in 30' intravenously
Cerebrospinal Fluid Pressure in Mm. Ringer Solution
Cc. Urine in 15 Min.
Cisternal puncture
0.23 gm. Na-Amytal
88.0 cc 50% Glucose
Na-Amytal 0.23 gm.
0.25 gm. Na-Amytal
Total urine since 11 45 280 cc.
Fluid cloudy 370 white cells/cu mm
Time 11 12 1 2 3 4 5 6 7 8 9 10 11
Pulse/min. 142 148 124 128 125 124 136 126 124 126 124 124 124 124 124 126 144 126 118 116 120 116 114 122 120
Resp./min. 34 28 22 22 16 17 22 22 16 20 17 16 16 14 16 19 17 24 20 26 27 26 20 22 16
Temp. °C. 36.8 36.3 37.3 36.3 36.2 36.7 37.5 38.0 37.3 37.3 37.3 37.4 37.6 37.4 37.3 37.6 38.4 38.4 37.8 37.7 37.6 37.4 37.4 37.4 37.5
Sucrose Experiment
Aug. 9, 1933 ♀ Dog 13.3 Kgm
8:55 am 0.7 gm. Na-Amytal (10%) intraperitoneally
160 cc. 50% Sucrose (6 gm/Kgm) in 30 min.
Cerebrospinal Fluid Pressure in Mm Ringer Solution
Cc. Urine in 15 Min.
Cisternal puncture
160 cc 50% Sucrose intravenously in 30 min
0.2 gm. Na-Amytal
11 15–2 15 Total urine = 600 cc. Sucrose = 78 gm (approx.)
0.2 gm. Na-Amytal
Shivering Movements Yawn
0.2 gm. Na-Amytal
0.15 gm. Na-Amytal
Fluid cloudy White cells 4600/cu mm
Time 10 a.m. 11 12 p.m. 1 2 3 4 5 6 7 8 9 10 11 12
Pulse 128 132 124 104 120 120 120 112 106 108 112 130 120 102 96 100 108 108 112 108 112 104 140 124 112 108 104 100
Resp. 19 20 16 20 26 34 20 20 20 21 22 24 20 18 15 14 14 14 14 12 14 16 24 26 12 12 14 14
Temp °C 36.3 36.8 36.1 37.3 37.6 37.9 37.7 37.4 37.5 37.5 37.7 38.0 38.1 37.6 37.2 37.1 37.5 37.7 37.5 37.5 37.3 37.2 37.9 38.3 38.4 38.1 37.9 37.5

Fig. 373.—Comparison of the effects on cerebrospinal fluid pressure of intravenous injections of hypertonic solutions of sodium chloride, glucose, and sucrose, showing that sodium chloride and to a lesser extent glucose cause a secondary increase in pressure which does not occur with sucrose. (From Bullock, Gregersen and Kinney.[15])

not explainable. Added to this is the observation that a number of dyes which diffuse easily from blood to lymph do not enter the spinal fluid at all. These facts suggest that the blood-spinal fluid barrier takes an active part in the distribution of substances between blood and serum.

In the recumbent position, the cerebrospinal fluid pressure in man averages 130 to 150 mm. of water, regardless of whether the pressure is measured in the cisterna magna or in the lumbar region. In the sitting position, the lumbar pressure rises to 200-250 mm. of water. No demonstrable changes are produced by altering the arterial pressure, but an increase in the venous pressure has an immediate effect. This may be demonstrated very simply by pressing on the jugular vein.

Because the cranial contents are enclosed in a rigid case, an increase in the intracranial pressure tends to set up a vicious circle. As the pressure rises, interference with the venous outflow retards absorption of spinal fluid and at the same time increases filtration because of a rise in the capillary pressure in the choroid plexuses. This situation may be produced by a cranial tumor or by swelling of the brain tissues as a result of trauma. Unless the vicious circle is broken at some point, the patient becomes comatose and finally succumbs. Relief of pressure is obtained with varying success by opening the skull, by removing fluid with lumbar or cisternal puncture and by increasing the tonicity of the blood.

The effect of alterations in the tonicity of the blood upon cerebrospinal fluid pressure was first demonstrated by Weed and McKibben.[146] They found that intravenous injections of water caused swelling of the brain and increased intracranial pressure, whereas the reverse was true with injections of hypertonic sodium chloride solution. Clinical experience with concentrated salt solution soon revealed that relief was only temporary and was followed by a subsequent rise in pressure far in excess of the original. From the discussion in the preceding pages, it is evident that the reason for this secondary rise lies in the fact that sodium chloride diffuses into the tissues, which therefore retain more water than was present before the injection. Concentrated glucose solutions have a similar although less extreme effect. With injections of concentrated sucrose, the secondary increase in pressure is entirely absent,[15] and this has been shown to be true also for sorbitol.[114] The molecular weight of sorbitol is one-half that of sucrose and therefore a given dose of 50 per cent solution of sorbitol is more effective in reducing the spinal fluid pressure than the same amount of sucrose.[114]

The differences in the effects of salt, glucose, and sucrose upon spinal fluid pressure in dogs may be seen in Fig. 373. Glucose and sodium chloride are partly stored in the tissues, but sucrose is rapidly excreted in toto, taking with it considerable quantities of body water. Of these three, therefore, sucrose is the most effective as a means of keeping down the cerebrospinal fluid pressure.

It should be emphasized that when concentrated solutions are given intravenously, the plasma volume is temporarily increased by a much greater amount than the volume of solution injected. For example, intravenous injection of 250 ml. of 50 per cent sucrose in twenty minutes into a dog weighing 20 kg. practically doubles the plasma volume. Sudden increases of this magnitude are very apt to embarrass the circulation, and therefore these solutions should in practice be given very slowly.

Evidence of impairment of renal function as well as of pathological changes in the kidney (swelling of the tubule cells with subsequent degenerative changes in the protoplasm and nucleus) has been observed in animals receiving large injections of hypertonic sucrose.[64, 66, 82] The changes are evidently reversible, for the histological picture returns to normal within seven to fourteen days after the last injection. The exact cause of the damage is not known. It may be either a direct effect of the sucrose on the kidney cells or an indirect effect resulting from sudden and large disturbances in the internal distribution of water and electrolytes and the rapid loss of both salt and water during the severe diuresis. There is some indication that the degree of damage depends upon the rate and amount of the injection of sucrose and upon the previous fluid and electrolyte balance of the animal. In dogs, the danger of impairing renal function is minimized by injecting the sucrose slowly (under 2 ml. per minute) and by maintaining the animals on a high salt diet.[67]

PART IX

THE KIDNEY

By Magnus I. Gregersen

CHAPTER LXXXII

THE KIDNEY

The kidney is so obviously concerned in the elimination of nitrogenous waste products that one might be inclined to regard it merely as an excretory organ. This view, however, does not do justice to its complex activities. For example, we have seen in the preceding chapter that the kidney is also involved in the maintenance of the water balance. Even this role appears to be merely a consequence of the kidney's chief function, namely, that of regulating the composition of the blood. Whereas urine formation may be accelerated by the ingestion of water or salt alone, there is usually little or no diuresis following the ingestion of isotonic sodium chloride. The kidney is influenced more readily by disturbances in the composition of the body fluids than by changes in the total water content of the body.

The kidney should be looked upon rather as a filter plant which not only removes the end products of protein metabolism (urea, sulfate, phosphate, etc.) and other waste products or foreign substances that may be dissolved in the plasma, but which also makes continual adjustments in the relative and absolute concentrations of the normal constituents of the plasma. In order to serve the body effectively in these capacities the filter plant must have a large turnover. It is estimated that the blood flow through the kidneys in man is about one liter per minute. This means that a volume equal to all the blood in the body flows through these organs every five minutes. Furthermore, it should be noted that the blood in its passage through the kidney must traverse two capillary beds in series. At least one-quarter of the fluid contained in the blood is filtered off in the first set of capillaries; nearly all of it is then returned to the blood stream in the second set after being subjected to what might be termed a "purification process" by the kidney cells. The volume of fluid subjected to this treatment every hour is greater by nearly three times than all the plasma in the circulation. By thus standing guard over the plasma composition, the kidney is to a very great extent responsible for the constancy of the "internal environment" of the body. It is not surprising therefore to find that disturbances in renal function may quickly manifest themselves in general bodily changes, such as edema, dehydration or toxemia. Since these conditions may also arise from other causes, it is often important clinically to determine whether or not renal function has suffered a change, and if so, to assess the nature and extent of renal damage. This requires an understanding, first, of the processes occurring in the normal kidney and the experimental methods by which they have been revealed, and second, a knowledge of the physiological

factors that control these processes. Only in this way is it possible to distinguish between cause and effect and to exercise sound judgment in the treatment of renal disease and allied conditions.

A. THE STRUCTURE OF THE KIDNEY

The truism that function is related to structure is nowhere more clearly illustrated than in the kidney. So much can be learned about the function of this organ from a study of its structure that a brief review of the anatomy of the renal elements concerned in urine formation is in order.

1. The Functional Unit

The Structure of the Nephron in Man.—The adult human kidney contains about 1,000,000 functional units known as nephrons. Each nephron consists of an unbranched tortuous tubule which at its origin in the cortex of the kidney is dilated to form a capsule (Bowman's capsule) enclosing a cluster of capillaries (the glomerulus). The latter structure is known as the renal or Malpighian corpuscle. In the vicinity of the Malpighian corpuscle the tubule undergoes a series of convolutions, then proceeds as a straight tubule for a variable distance into the medulla of the kidney; here it makes a sharp bend returning again to the vicinity of the same corpuscle to undergo another series of convolutions before emptying into a collecting tubule. Many of the latter join together to form a collecting duct, which proceeds in a straight course through the medulla to the pelvis of the kidney. In the order mentioned, the various parts of the tubule are known as (1) the proximal convoluted tubule or proximal segment, (2) the straight segment or loop of Henle, (3) the distal convoluted tubule or distal segment, and (4) the collecting tubule. Although this division is based merely on external configuration and differences in cell structure, it is justified also by differences in function.

The location of both the proximal and distal convoluted tubules in close proximity to the renal corpuscle of the same nephron is the result of embryological development.[18] A tubular anlage first appears as an S-shaped renal vesicle near the end of each branch of the developing collecting ducts. One end of this S-shaped structure connects with the collecting duct, while the other forms an invaginated bowl which is early invaded by a cluster of blood vessels, the future glomerulus. The tubule is thus anchored at one end by the glomerulus and at the other by the adjacent collecting duct. Between the developing convolutions of the proximal and distal ends, which lie in a nest around the renal corpuscle, a straight segment grows into the medulla to become the loop of Henle.

The Renal Corpuscle (see Fig. 375).—The general structure of the renal corpuscle and its true relation to the uriniferous tubule were demonstrated by William Bowman in 1842.[13] In the adult kidney the renal corpuscle measures about 0.2 mm. in diameter. The capillary tuft or glomerulus is enclosed by a double-walled sac (Bowman's capsule) created as described above by the invagination of the dilated blind end of the tubule. The space between the two layers of this capsule is continuous with the lumen of the tubule. The inner or visceral layer of the capsule is not merely a pouch, but adheres closely to the glomerular capillaries which are "completely covered by epithelium, just as a finger is covered by a glove."[139] It consists of very thin epithelial cells, hardly distinguishable except by their nuclei, and rests upon a structureless basement membrane which is directly in contact with the endothelium of the capillary loops. The blood in the capillaries is thus separated from the capsular cavity by (a) the endothelial wall of the capillaries, (b) the basement membrane, and (c) the visceral epithelium. Normally they form an extremely thin membrane with a total thickness of only 0.001 mm.; but in glomerular nephritis and other forms of renal disease, the various layers undergo thickening and the capsular cavity may become filled with proliferating epithelial

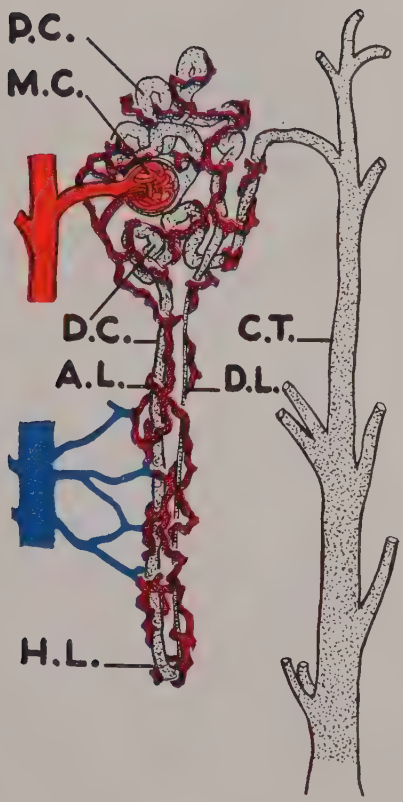


Fig. 374.—Diagram of the nephron with its blood vessels. *M.C.*, Malpighian corpuscle; *P.C.*, proximal convoluted tubule; *D.L.*, descending limb, showing the thin segment; *H.L.*, loop of Henle; *A.L.*, ascending limb; *D.C.*, distal convoluted tubule; *C.T.*, collecting tubule. (Redrawn from Cushny by A. R. Munro.)

cells. The outer wall or parietal layer of the capsule is made up of flattened epithelial cells which change to cuboidal at the junction with the neck of the proximal convoluted tubule. The glomerulus contains about 50 capillary loops, each 0.5 mm. in length. Vimtrup[139] finds no evidence for anastomoses or short circuits between the capillary loops.

The Renal Tubule.—The proximal convoluted tubule is lined with a single layer of cuboidal or columnar epithelium. The cells are distinguishable from those in other parts of the tubules principally by the presence of a "brush border" on the luminal margin. They are coarsely granular, contain large nuclei, and show characteristic cytoplasmic striations extending vertically from the base of the cells. In the resting state the lumen is practically obliterated, but during active secretion it becomes enlarged (see Fig. 376); the cells are then somewhat flattened. Many attempts have been made to relate the changes in microscopic appearance of the cells with activity, but the results have not been helpful in elucidating the secretory mechanism. The studies with dyes are also inconclusive, some showing that granules are formed in the basal portion of the cell and extruded into the lumen, others showing that the granules are formed near the lumen and transported toward the basement membrane. According to the prejudices of the investigators, these observations have been accepted as evidence of secretion from the blood stream into the lumen or of reabsorption from the tubular fluid.

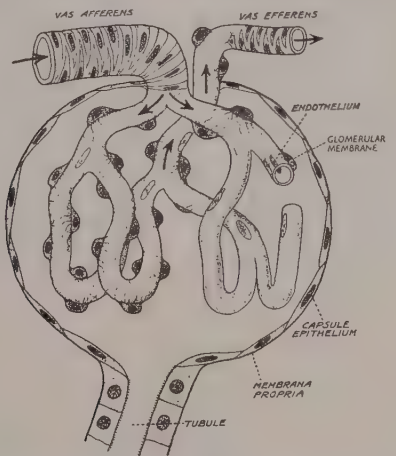
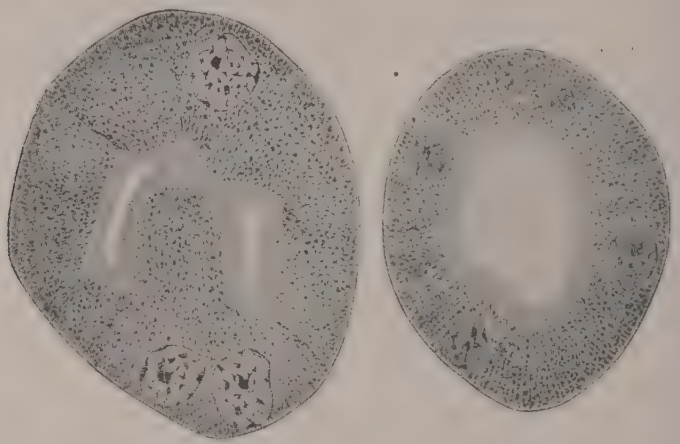


Fig. 375.—Diagram of a *Malpighian Body.* This consists of a tuft of capillaries, the glomerulus, within an invaginated membrane, *Bowman's capsule,* which forms the head of the *tubule.* Note that the capsule epithelium is reflected over the outside of the capillaries of the glomerular tuft. There are in reality many more capillary loops than are shown. Blood enters the glomerulus from the *vas afferens,* and leaves it by the *vas efferens.* The former is definitely larger than the latter. (After v. Möllendorff from Winton and Bayliss.[151])

The first portion of the descending limb of the straight segment is microscopically similar to the proximal segment except for the absence of the brush border. At a variable distance along its course this part of the tubule suddenly decreases in diameter from 0.05 or 0.06 mm. to 0.015 or 0.02 mm. The difference in size is due chiefly to the presence of flatter cells (pavement epithelium), the lumen remaining roughly the same. The thin segment continues for some distance along the ascending limb where the cuboidal cells again make their appearance. The thin medullary segment of the nephron is a distinctive feature of the mammalian kidney and is not found in lower animals, with the exception of some birds in which it is poorly developed. It appears to have a special function in connection with the reabsorption of water from the tubular fluid. Its length is variable, depending upon the length of the entire medullary segment itself. The cells of the distal convoluted tubules are similar to those of the thick portion of the ascending limb. They possess no brush border, and the granulations are finer than in the proximal segment. These granulations disappear altogether in the collecting tubules where the cytoplasm is clear and the nuclei very distinct by contrast.

Macula Densa and Polkissen.—Recent anatomical studies on the kidney have revealed special modifications of the smooth muscle cells of the afferent arteriole into cells of an epithelioid nature. There is also a change in the epithelium of the distal tubule where these two structures are juxtaposed. In addition, certain cells form an asymmetrical pad at the arteriolar-capsular junction. This so-called polar pad or *polkissen* is made up of small cells which are interposed between the macula densa and the glomerular membrane. The epithelial cells of the distal tubule lying in contact with this region of the arteriole tend to be columnar rather than low cuboidal, and their nuclei are densely crowded. For the latter reason this area of cells has been termed the *macula densa.* The cells of the *polkissen* and the adjacent *macula densa* are allegedly supplied with nerve fibers and are suspected of having functional significance. For details the reader should consult the reviews by Homer Smith.[128, 130]



A. *B.*

Fig. 376.—Cross-sections of convoluted tubules from kidney of rat. *A*, during slight secretion; *B*, during maximal secretion. (From Sauer.)

Dimensions of the Nephron.—After the kidney has been macerated in hydrochloric acid, it is possible to tease out the intact nephron. When uncoiled, it measures 40 to 60 mm. in length, the variation depending largely upon the extent of the thin segment. Generally speaking, the length of the latter is determined by the location of the renal corpuscle from which the tubule arises and by the proportion of the straight segment present in the medulla. If the renal corpuscle lies in the outer region of the cortex, the straight segment of the nephron usually penetrates the medulla only a short distance, whereas tubules arising from corpuscles situated deeper in the cortex may have straight segments that run the entire depth of the medulla.

Reliable figures for the total number of glomeruli in the kidney have been obtained by Vimtrup.[139] The kidneys were injected through the blood vessels with Prussian blue reagents to stain the glomeruli, macerated in acid and the cortex carefully separated from the medulla.

TABLE CXIX

SPECIES	WEIGHT OF FRESH KIDNEY	NUMBER OF GLOMERULI	
Man, child	?	887,399	estimate
Man, child	?	955,251	total count
Man, adult	?	833,992	estimate
Man, adult	143 grams	867,177	estimate
Man, adult	165 grams	1,233,360	estimate
Dog, 8 kg.	29 grams	407,155	estimate
Dog, 12 kg.	38 grams	507,913	estimate

In a few cases he made total glomerular counts which were found to check closely with the estimates derived from a sample count and the total mass of the cortex. A summary of his results on man and the dog is shown in Table CXIX. From the diameter, length, and number of the capillary loops, Vimtrup calculates that the filtration surface in each glomerulus in the human kidney is equal to 0.78 sq. mm. Since each kidney in man contains about 1 million glomeruli, the total filtration surface in both kidneys is at least 1.5 square meters.

It is useful to compare this with the total surface exposed in the tubules. The size of the tubular lumen varies considerably in different segments and, as we have noted, also shows changes with activity; but if it be assumed that the average diameter is 0.002 mm. and the average length 50 mm., the interior surface of each tubule is 3 sq. mm. The combined tubular surface in both kidneys is therefore in the neighborhood of 6 square meters, or four times as large as the filtration surface in the glomeruli.

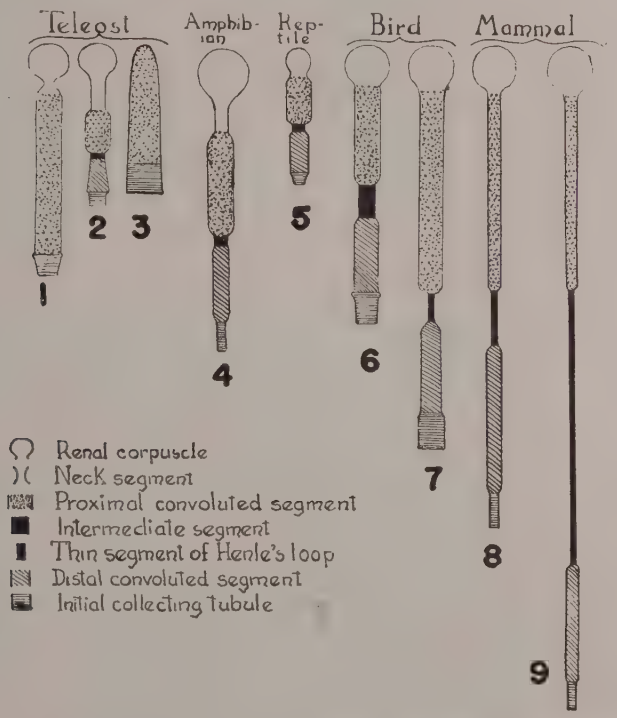


Fig. 377.—Diagram from Marshall showing relative development of uriniferous tubule in various groups of animals. (Redrawn by A. F. Munro.)

The Structure of the Nephron in Lower Animals.—The nephron of the mammal is a fairly complex structure in which the processes occurring in the various morphologically distinct segments cannot be segregated for independent study, at least in the intact unanesthetized animal. In some of the lower animals, however, the situation is simplified to such an extent that it offers opportunities for investigating separately the function of the homologues of certain segments in the mammalian tubule.[90] Some of the possibilities which nature thus presents are shown diagrammatically in Fig. 377. The proximal convoluted tubule (distinguished by epithelial cells with brush borders) is the only segment which occurs in all classes of vertebrates. Particular interest attaches to the sculpin (No. 1) and to the toadfish and goosefish (No. 3); in the two latter the nephron consists only of the proximal segment,

and in the former of proximal segment and glomerulus. In the amphibia, reptiles, and most of the birds, the thin segment or loop of Henle is lacking. This segment, as we have already pointed out, is a distinctive mammalian differentiation, which appears to be associated with the capacity of the kidney to form hypertonic urine. Although it is by no means certain that a given segment functions in exactly the same way wherever it occurs in the vertebrate scale, there is no doubt that the identity of the cell structure at least lends considerable weight to the belief that the potential function of, let us say, the proximal segment is essentially the same in all forms. It should be pointed out, however, that the predominant process occurring in a segment may, to a large extent, be conditioned by the demands of the situation. In the glomerular forms (mammals, etc.) the function of the proximal segment is mainly one of reabsorption. In the aglomerular fish it is purely secretory. There is evidence that a similar reversal of function may occur in mammals after glomerular function has been suppressed by glomerular nephritis. At least one should bear in mind the possibility that tubular functions may, under pathological conditions, show adaptations which alter the process by which urine is formed.

2. Blood Supply

In proportion to its size, the kidney possesses a rich blood supply. The latter is remarkable for its arrangement with relation to the nephron (see Fig. 374). Upon entering the hilus of the kidney, the renal artery breaks up into four or five large branches which run to the boundary zone between the cortex and the medulla where they turn to form the arciform arteries. These give rise to smaller branches (interlobular arteries) which radiate into the cortex of the kidney and along their course give off smaller vessels, the *afferent arteries*, each of which breaks up into a small capillary tuft, the glomerulus, consisting of about 50 capillary

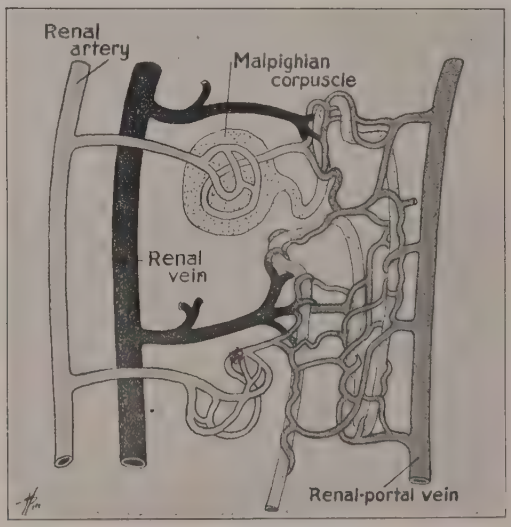


Fig. 378.—Diagram of blood supply of Malpighian corpuscle and of convoluted tubules in amphibian kidney. (Redrawn from Cushny.)

loops and surrounded by Bowman's capsule. The capillaries are twisted and tortuous, but do not anastomose at any point along their course. At the vascular pole of the capsule they again join to form an *efferent artery* which is about one-half the diameter of the afferent (see Fig. 375). It should be noted that changes in the caliber of these vessels can exert profound effects on the glomerular circulation. Upon leaving the renal corpuscle, the efferent artery soon breaks up into another capillary network surrounding the tubules and forming their sole blood supply. In passing through the kidney, the blood must accordingly traverse

two sets of capillaries. In the outer layers of the cortex the efferent artery usually supplies the proximal and distal convoluted tubules of the same nephron. Deeper in the cortex, especially near the margin of the medulla, many of the efferent arteries may not subdivide immediately but take a straight course into the medulla where they form capillary networks of elongated meshes around the straight segments. Hence the blood supply of a tubule is not necessarily derived even in part from the glomerulus of the same nephron. Furthermore, the tubular capillaries from adjacent efferent vessels tend to anastomose. The tubular capillaries empty into a venous system which is more or less confluent with the arterial system.

Homer Smith[130] in a review of the renal circulation points out that a number of anatomists and pathologists have found exceptions to the classical concept which postulates that the blood supply of the tubules is derived entirely from the efferent glomerular arterioles. He concludes that direct arterial connections with the peritubular capillary plexus apparently occur to a small extent even in the normal kidney. These have been described as arising from the interlobular and subcortical arteries and from an occasional small branch of the afferent arteriole. Furthermore the arterio-venous anastomoses found in the kidney, may, as Spanner suggests, represent another channel by which the tubular capillaries can receive blood when the glomerular circulation is arrested.

Renal Blood Supply in Lower Animals.—The description of the renal circulation given above does not hold for reptiles, amphibians and fish. Since many of the deductions as to the function of the nephron in mammals have been drawn from experiments on these lower forms, especially the frog, it is well to note the differences in their renal blood supply.

In the frog, the glomerulus and the tubules are supplied with blood by the renal artery, as is the case in the mammal, but the tubules are also supplied with some of the blood coming from the lower extremities and the trunk through a vessel which has no counterpart in the mammal—the renal-portal vein (see Fig. 378). The blood which supplies the tubules is therefore a mixture from the glomerulus and the renal portal system. By ligating the renal artery, the arterial blood supply to the glomerulus is shut off while the tubules are still supplied by the renal portal vein, thus presumably providing a preparation on which tubular function can be studied separately. All investigators have not agreed, however, that glomerular function is entirely suppressed by this procedure. In aglomerular fish (toadfish and goosefish) the blood supply of the nephron is entirely venous. The development of the arterial supply appears to occur only in the forms that possess glomeruli.

3. Nerve Supply

The kidney is supplied with nerve fibers from the sympathetic by way of the splanchnics and from the parasympathetic by way of the vagi. Before entering the kidney the fibers form a network, the renal plexus, overlying the renal vessels, from which they can be traced along the arteries to all parts of the kidney. Both motor and sensory endings occur in the afferent and efferent arterioles, and fibers have also been found on the glomerular capillaries as well as in and among the cells of the tubules. Nevertheless, it has not been possible to demonstrate that stimulation of the renal nerves has any specific secretory effect. The influence of the nerves on urine formation appears to be produced entirely through their vascular effects. Furthermore, the nerves do not seem to be essential for urine formation since the denervated[73] or re-implanted[105] kidney apparently functions quite normally.

B. THE MECHANISM OF URINE FORMATION

1. Theories of Renal Function

Bowman's Theory.—The modern history of the kidney began with the observations of an English surgeon and physiologist, Sir William Bowman, whose paper *On the Structure and Use of the Malpighian Bodies of the Kidney, with Observations on the Circulation through that Gland,* published in 1842,[13] had a profound effect on the subsequent development of renal physiology. Bowman evolved a theory of urine formation based entirely on his anatomical findings. He reasoned that the glomerulus probably forms a watery fluid since the type of epithelium which embraces the capillary tuft is clearly de-

signed for the easy escape of fluid from the blood stream. Furthermore, the arrangement of blood vessels in the Malpighian corpuscles (large afferent and small efferent artery) appears to effect a retardation of blood flow. On the other hand, the similarity of the thick epithelial cells in the tubules to those found in other glands led him to believe that the tubules have a secretory function. In short, he postulated that the urinary products, such as urea, are secreted by the tubules, and that the fluid formed in the glomeruli serves only to carry away the secreted materials.

Ludwig's Mechanical Theory.—Only two years after the publication of Bowman's paper, Carl Ludwig[84, 86] brought out the so-called "mechanical theory" by which he attempted to explain urine formation on a purely physical basis. According to this theory the hydrostatic pressure in the glomerular capillaries causes filtration of a large amount of dilute fluid containing all the urinary constituents; during its passage down the tubules, this fluid is concentrated by the diffusion of water into the tubular capillaries, the latter process being the result of a difference in osmotic pressure between the tubular fluid and the blood. Hoppe-Seyler later proved that this explanation of the reabsorption was indequate by showing that the osmotic pressure of the urine may be considerably higher than that of the blood leaving the kidney. Nevertheless, a large body of evidence was collected, mostly by Ludwig and his pupils, which demonstrated that urine flow was dependent on physical forces.[20] It was found, for example, that lowering of either the general blood pressure (e.g., by stimulation of the vagus in the neck, or by bleeding) or the renal blood pressure alone (partial occlusion of the renal artery) always reduced the urine flow. The same result was obtained by raising the ureteral pressure which at 50-60 mm. of Hg stopped urine secretion completely. On the other hand, the urine flow was augmented by raising the blood pressure with generalized vasoconstriction (provided the renal nerves were severed!) or with intravenous injections. The effect of partial occlusion of the renal vein did not, however, fall into line with the physical theory; instead of increasing the urine flow as one would expect (back pressure should tend to raise the glomerular capillary pressure, and therefore enhance filtration), this procedure accomplished quite the opposite.[63]

Heidenhain's "Secretion" Theory.—The mechanical theory of Ludwig was vigorously opposed by Heidenhain,[63] who formulated instead a "secretory" theory which was essentially an elaboration of Bowman's concept. According to Heidenhain, all constituents of the urine are formed by "vital" activity of the cells. The glomerulus secretes water and salt and the tubules secrete special urinous products, such as urea, and may also when required secrete water. Reabsorption in the tubules is completely excluded. Heidenhain's experimental evidence was drawn chiefly from a study of the secretion of dyes. One of his oft-mentioned experiments consisted of showing that indigo carmine is secreted by the proximal tubules of the rabbit when the blood pressure is so low that urine flow has ceased entirely. Under these conditions it was assumed that the dye could not have entered the tubules through the glomerulus since the latter was presumably nonfunctional. The interpretations which he placed upon his results were not universally accepted, and certainly the above experiment provides less convincing proof of secretion than that established by other methods to be described presently. Furthermore, even if the tubules do secrete a foreign

dye, it does not necessarily follow that they deal with normal constituents of the urine in the same manner. One of Heidenhain's chief objections to the mechanical theory was that it called for the filtration of what he regarded as unreasonably large amounts of fluid in order to account for the quantity of urea excreted. He pointed out that if the concentration of urea in the glomerular filtrate is 0.05 per cent, the daily excretion 35 grams and the urine volume 2 liters, then the mechanical theory requires the filtration of 70 liters and the reabsorption of 68. Now as a matter of fact, this is a rather low estimate (see below) and, furthermore, direct collection of capsular fluid from the individual glomerulus of the frog (Richards) shows that it is entirely within reason. Heidenhain also argued that the effect of obstructing the renal vein was a clear indication that blood flow and not blood pressure is the determining factor in regulating urine formation. Regarding the kidney as a true secretory gland similar to the submaxillary, he chose to interpret the results of Ludwig's experiments relating blood pressure to urine flow as being merely the effects of changes in the blood flow on the supply of oxygen and other nutrients to the secreting cells. Thus it would seem that although Heidenhain brought forth relatively little direct evidence in support of his secretory theory, his criticisms put the mechanical theory on the defensive.

That urine formation is not strictly comparable to the process of secretion in the salivary glands is evident from the following: (1) The submaxillary gland secretes only when stimulated through its nerves or by appropriate chemical stimuli (e.g., pilocarpine). When its connections with the central nervous system are severed, secretion stops. The kidney is in this respect quite different since stimulation of the renal nerves is unnecessary for its activity. Furthermore, it continues to secrete after complete denervation. (2) It was shown many years ago by Ludwig[85] that stimulation of the chorda tympani results in a secretion of saliva even when the blood pressure is zero. This phenomenon cannot be reproduced in the kidney. (3) Still more striking is the difference revealed by the maximal secretion pressures which the glands can produce. In the submaxillary gland this may be from two to three times greater than the existing arterial blood pressure,[85] whereas in the kidney it rarely exceeds one-half the blood pressure.[134] (4) The response of the submaxillary gland to a uniform stimulus is uninfluenced by dilution or concentration of the blood within the physiological range. The kidney, on the other hand, is remarkably sensitive to such changes. (5) The submaxillary gland secretes special substances (mucin, etc.) which are not found in the plasma. In contrast to this, the urine contains no special substance which is not also present in the blood. (6) Saliva is always more dilute with respect to crystalloids than the plasma from which it is derived. The concentration of the urine is not fixed with relation to the blood but may be either higher or lower, according to the requirements.

It is also instructive to compare urine formation with lymph formation, which, so far as we know, is a purely mechanical filtration process. (1) Nerve stimulation affects both urine and lymph flow only so far as it causes vascular changes. (2) The maximal secretion pressure is in both cases less than the arterial blood pressure. (3) All the constituents in lymph and urine may be found as such in the plasma. (4) A significant difference appears, however, if one compares the relative concentration of various substances in these fluids

with the relative concentrations in the plasma. The composition of lymph is in every respect similar to that of plasma except that it contains less protein.* In the urine, however, some of the plasma constituents are present in a much lower concentration than in plasma or may be entirely absent (e.g., glucose), whereas others (e.g., creatinine) may be raised to one hundred times their value in plasma. In view of these facts it is obvious that although urine formation resembles both salivary secretion and lymph formation in certain particulars, it cannot be relegated entirely to one category or the other. A complete theory of kidney function must include some features from both.

Cushny's "Modern" Theory.—A compromise is found in the so-called modern theory of Cushny.[20] This theory incorporates filtration of a protein-free fluid in the glomerulus and selective reabsorption in the tubules. The latter process is not explained by passive diffusion as in Ludwig's theory, but as an active process depending upon work done by the tubule cells. It should be noted also that the modern theory as formulated by Cushny excludes secretion, but evidence brought forth in recent years has required its inclusion at least for the excretion of certain substances, notably phenol red. The outstanding feature of the modern theory is that it attempts to simplify the process of reabsorption. Cushny noted that the tendency for a substance to be excreted by the kidney is roughly inversely proportional to its importance as a constituent of a normal perfusion fluid. This may be seen in Table CXX which gives the usual concentrations of a number of substances in plasma and urine. Substances such

TABLE CXX

(From Cushny[20])

	BLOOD PLASMA PER CENT	URINE PER CENT	CHANGE IN CONCENTRATION IN KIDNEY
Water	90-93	95	—
Proteins, fats, and other colloids	7-9	—	—
Glucose	0.1	—	—
Na	0.30	0.35	1
Cl	0.37	0.6	2
Urea	0.03	2	60
Uric acid	0.004	0.05	12
K	0.020	0.15	7
NH_4	0.001 (?)	0.04	40
Ca	0.008	0.015	2
Mg	0.0025	0.006	2
PO_4	0.009	0.15	16
SO_4	0.002	0.18	90
Creatinine bodies	0.001 (?)	0.075	75

as sulfate, creatine, urea and ammonia, which may be classed as waste substances, are evidently concentrated in the kidney to a great extent, whereas the necessary constituents of the plasma, such as glucose and sodium chloride, are either present in the urine in low concentration relative to their plasma levels or are entirely absent. On the other hand, if the latter substances, of which we may take glucose as an example, are present in the plasma in excess of their normal concentrations (i.e., above a certain "threshold" value), they are excreted. From these facts Cushny evolved the idea that the concentration in

*There is a slight difference in the electrolyte distribution due to the Donnan equilibrium.

which various useful substances are reabsorbed by the tubule cells has a definite limit, fixed for each substance according to the concentration at which it is present in a "normal" plasma. The substances that behave in this manner he called "threshold substances," and the remainder, which the tubule cells reject altogether, he called "no-threshold" substances. Thus he conceived of the reabsorption process as a blind process and urine as the inevitable result of the changes wrought in the capsular fluid by abstraction from it of a Ringer-Locke solution.

The data presented in Table CXXI will serve to show how he arrived at this conclusion. If it be assumed that all substances in the urine are derived only from the glomerular filtrate, and further that at least one substance in the filtrate is not reabsorbed by the tubules, the composition of the reabsorbed fluid may be calculated. Cushny took it for granted that sulfate is a strictly no-threshold substance. Therefore, on the basis of the plasma concentration of sulfate, he estimated that the amount present in 1 liter of urine must have been

TABLE CXXI

(From Cushny[20])

	90 LITERS PLASMA CONTAIN		83 LITERS FILTRATE CONTAIN	82 LITERS REABSORBED FLUID CONTAIN		1 LITER URINE CONTAINS	
	PER CENT	TOTAL		PER CENT	TOTAL	PER CENT	TOTAL
Water	92	83.0 liters	83.0 liters	—	82.0 liters	95	950 ml.
Colloids	7.5	6750.0 Gm.	—	—	—	—	—
Glucose	0.1	90.0 Gm.	90.0 Gm.	0.11	90.0 Gm.	—	—
Sodium	0.3	270.0 Gm.	270.0 Gm.	0.32	266.5 Gm.	0.35	3.5 Gm.
Chloride	0.37	333.0 Gm.	333.0 Gm.	0.4	327.0 Gm.	0.6	6.0 Gm.
Urea	0.03	27.0 Gm.	27.0 Gm.	0.008	7.0 Gm.	2.0	20.0 Gm.
Uric acid	0.004	3.6 Gm.	3.6 Gm.	0.003	3.1 Gm.	0.05	0.5 Gm.
Potassium	0.02	18.0 Gm.	18.0 Gm.	0.02	16.5 Gm.	0.15	1.5 Gm.
Phosphate	0.009	8.1 Gm.	8.1 Gm.	0.0008	6.6 Gm.	0.15	1.5 Gm.
Sulfate	0.002	1.8 Gm.	1.8 Gm.	—	—	0.18	1.8 Gm.

obtained from 90 liters of plasma or, that is, from 83 liters of protein-free filtrate. The amounts of the various constituents in this filtrate are known from their plasma concentrations, and by subtracting from these amounts the quantity excreted in 1 liter of urine, he derived the composition of the 82 liters which have been reabsorbed. Except that this fluid contains some urea and uric acid, its composition is very similar to that of a Ringer-Locke solution.

On first sight this seems to be an attractive simplification of tubular activity since it makes the kidney an organ with a fixed and predictable function. It does not, however, explain the actual mechanism whereby the tubule cells transfer substances against concentration gradients any more than did the secretion theory of Heidenhain. As a working hypothesis Cushny's theory has undoubtedly been of great service, but it should be pointed out that the investigations of the past decade have shown the theory to be incorrect in several respects. The reabsorption of water, glucose, chloride, phosphate and other substances are relatively independent processes, and several of the waste products which Cushny regarded as no-threshold substances are in reality partially reabsorbed. Furthermore, tubular excretion of certain substances can no longer be denied.

In view of these facts, it is a hopeless task at present to attempt to explain urine formation by any particular theory of renal function. Rather must we examine the facts and remain agnostic when these facts fail to provide a clear-cut explanation of the mechanism involved.

2. Function of the Glomerulus

We have already noted that Ludwig and his school demonstrated in a variety of ways that the rate of urine flow varies as the renal blood pressure. Viewed strictly, their evidence does not actually prove the existence of a filtration process in the kidney, much less that filtration occurs specifically in the glomerulus. These were suppositions based on the structure of the glomerulus, and it was a long time before unequivocal proof could be adduced to place glomerular filtration beyond cavil. The weakness in Ludwig's experiments lay in the fact emphasized by Heidenhain[63] that blood pressure and blood flow go hand in hand; that the changes in blood flow rather than the changes in blood pressure might be responsible for the observed variations in the rate of urine formation. Partial occlusion of the renal vein seemed to constitute a crucial test, for in this case the glomerular capillary pressure would rise while the blood flow would fall. The resulting decrease in the rate of urine formation was interpreted by Heidenhain to be clear proof that blood flow was the important factor. Ludwig, on the other hand, maintained that the engorged renal veins pressed upon the tubules to such an extent that the back pressure in the capsular fluid counterbalanced the effect of an increased glomerular pressure. After a period of controversy lasting nearly forty years, the question was finally settled in 1922 by the experiments of Richards and Plant.[108] A rabbit's kidney was perfused from a pump which kept the blood flow constant in spite of changes in the renal blood pressure. Under these conditions partial occlusion of the renal vein caused the urine flow to accelerate. This observation was confirmed by Dreyer and Verney[24] on the isolated dog's kidney. Recently Winton[148, 149] has devised a simple experiment which demonstrates in a direct manner that Ludwig's original interpretation of the effect produced by venous obstruction is correct. The intraureteral pressure is first raised by making the kidney secrete against a column of fluid. This in itself reduces the urine flow; but if the venous pressure is now increased, more urine is formed, provided the venous pressure does not exceed the ureteral pressure. Furthermore, if the ureteral pressure is gradually raised when the urine flow has already been reduced by partial obstruction of the vein, there is no further reduction in urine flow until the ureteral pressure exceeds the venous pressure. These experiments demonstrate in no uncertain fashion that physical forces are of fundamental importance in the formation of urine.

Glomerular Filtration.—According to the modern theory as enunciated by Cushny, the glomerulus forms a protein-free fluid by the simple process of filtration. Positive proof that this is the case requires the experimental demonstration (1) that the glomerular membrane is impermeable to the plasma proteins, (2) that the capsular fluid is in every respect identical with an ultrafiltrate of plasma, and (3) that the forces acting across the glomerular membrane are adequate to account for the formation of a protein-free capsular fluid. Through the efforts of Professor A. N. Richards and his colleagues, who have developed delicate micromethods for collecting (see Fig. 379) and

analyzing the capsular fluid from frogs, complete proof of glomerular filtration in the amphibia is now available. Their results will be considered before reviewing the less direct evidence for glomerular filtration in the mammal.

Glomerular Filtration in the Frog.—The semipermeable nature of the glomerular membrane of the frog was first demonstrated directly by Wearn and Richards.[144] They found that the capsular fluid normally is not only protein-free but contains glucose and chloride in approximately the same concentrations as the plasma. Since the latter was found to be true even when the bladder urine contained no glucose or chloride, the experiments also demonstrated that both of these substances may be reabsorbed by the tubules. In a series of investigations, which for their sheer elegance can hardly be rivaled in renal physiology, Richards and his co-workers have extended these observations to show that the composition of the capsular fluid is essentially identical with an ultrafiltrate of the plasma. Comparisons have been made on the basis of

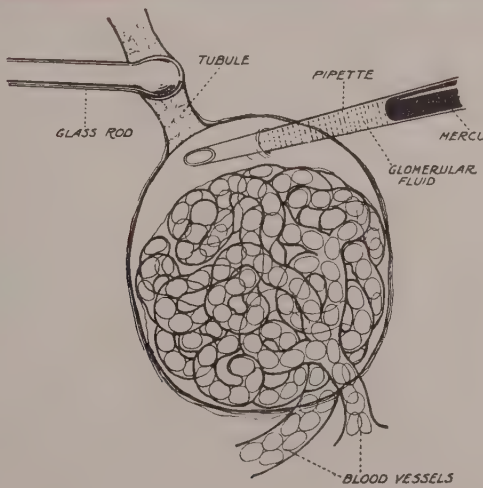


Fig. 379.—Diagrammatic representation of Richards' method of obtaining a sample of glomerular fluid from Bowman's capsule in the frog. A very fine pipette (7 to 15 μ diam.), connected with a reservoir of mercury and filled with mercury up to its tip, is thrust through the wall of the capsule, and fluid is withdrawn from the capsular space by lowering the mercury reservoir. The tubule is blocked by pressing on it with a fine glass rod, so that no fluid can be sucked back into the capsule. (From Winton and Bayliss.[121])

total molecular concentration (determined by Barger's vapor pressure method), electrical conductivity, chloride, inorganic phosphate, glucose, uric acid, creatinine and urea.[110] Experiments have also been made with phenol red and inulin. The only differences between the capsular fluid and plasma collected simultaneously were found in the analyses of chloride and phenol red. The former is slightly higher in the capsular fluid, but this is in accord with the Donnan equilibrium. In the case of phenol red, the unequal distribution is explained by the fact that about 30 per cent of this dye is combined with plasma proteins and is therefore unable to diffuse into the capsular fluid. The diffusible fraction, however, distributes itself in equal concentration between plasma and capsular fluid. The observations on inulin are of especial importance since

the capacity of the glomerular membrane to let this substance through is a fundamental assumption on which much of the experimental work on the mammalian kidney rests (see page 1118). In spite of its large molecular weight (5000), inulin distributes itself in the same concentration between blood and capsular fluid. In the face of such an impressive volume of evidence, it is impossible to avoid the conclusion that the frog's glomerular urine is merely a filtrate of plasma. There is no indication whatever that the glomerulus is capable of carrying out active secretion.

The forces concerned in the formation of capsular fluid in the frog have also been measured. In this species the plasma colloid osmotic pressure varies a good deal, the average being about 5 cm. of water. Is the glomerular capillary pressure sufficient to overcome this osmotic pressure? The measurements made by Hayman[62] indicate that the hydrostatic pressure is more than adequate to effect filtration. This may be seen in Table CXXII which represents a summary of Hayman's data.

TABLE CXXII

PRESSURES DETERMINING FILTRATION IN THE GLOMERULUS OF THE FROG'S KIDNEY

	PRESSURES (IN CM. H_2O)	
	RANGE	AVERAGE
Glomerular capillary blood pressure	10.0 to 27.0	20.2
Plasma colloid osmotic pressure (Churchill, Nakasawa and Drinker)	1.5 to 13.4	5.3
Filtration pressure	8.5 to 13.6	14.9

Hayman's technique was in principle similar to the cuff method of estimating blood pressure in man, and may be described briefly. A sharp-pointed micropipette was inserted into Bowman's capsule and connected with a manometer system (see Fig. 379). The neck of the proximal tubule was located by injecting colored saline, then closed with a glass rod. Thus the capsule served as a cuff in which the pressure required to occlude the capillaries could be measured. By this method the average glomerular capillary pressure was found to be 54 per cent of the existing aortic pressure.

The rate of filtration in individual glomeruli of the exposed kidney of the frog has been observed to vary from 1 to 3 or 4 c.mm. per hour. Each kidney in the frog contains some 2,000 glomeruli. Consequently, the total filtration rate in both kidneys of these animals is from 4 to 16 ml. per hour. Richards states that this is ten to twenty times greater than the urine flow. It is presumed that the rate of filtration is even higher in normal animals.

Glomerular Filtration in the Mammalian Kidney.—Unfortunately, the direct evidence obtained on the frog cannot be duplicated in the mammalian kidney because the glomeruli are located too far beneath the surface of the organ. There is, however, a sufficient amount of indirect evidence to indicate that the function of the glomerulus in warm-blooded animals is also purely a matter of filtration.

The limit of permeability of the mammalian glomerular membrane is defined with considerable sharpness by the recent experiments of Bayliss, Kerridge and Russell.[8] They followed the urinary excretion of a variety of proteins ranging in molecular weight from 35,000 (egg albumen) to 5,000,000 (hemocyanin) in anesthetized cats and rabbits and in the isolated dog's kidney. A summary of their observations is given in Table CXXIII. It is apparent from these data

that molecular size determines whether or not a protein escapes through the glomerulus. Hemoglobin, with a molecular weight of 68,000, appears to be on the borderline, since it is excreted only when present in the plasma in high concentration. The proximity of serum albumin to the limit of impermeability clearly explains why this serum protein is the first to appear in the urine when the kidney has been damaged temporarily by anoxemia, or permanently by renal disease. It was also noted by these investigators that the normal impermeability of the isolated dog's kidney to serum albumin was not altered or impaired by a period of perfusion with a protein, such as egg albumen which passes through the glomerulus. In view of these facts it must be concluded that capsular fluid in the mammal is normally protein-free. Furthermore, the capsular fluid is probably identical with an ultrafiltrate of serum since it is unthinkable that any of the crystalloid constituents could be retained by a membrane that only discriminates against proteins on a basis of their molecular size.

TABLE CXXIII

RELATIONSHIP BETWEEN MOLECULAR WEIGHT OF PROTEINS AND THEIR ABILITY TO PASS THE GLOMERULUS (From Bayliss, Kerridge and Russell[8])

	MOLECULAR WEIGHT OF PROTEIN*
Proteins excreted:	
Gelatin	35,000
Bence-Jones	35,000
Egg albumen	34,500
Hemoglobin	68,000
Proteins not excreted:	
Hemoglobin	68,000
Serum albumin	67,500
Serum globulin	103,800
Edestin	208,000
Casein	188,000
Hemocyanin (Helix)	5,000,000

*Determined by ultracentrifugation method.

Experiments on the isolated dog's kidney in which tubular function has been suppressed either with cyanide or by cooling lend further support to the belief that the fluid formed in the glomerulus is essentially the same as protein-free plasma. Starling and Verney[135] observed that the addition of cyanide to blood pumped through the kidney caused an increase in the volume of urine secreted. The concentration of chloride in the urine rose, whereas the amount of sulfate and urea fell, in percentage as well as in terms of the total amount excreted. In fact, the composition of the urine resembled closely that of deproteinized plasma. Similar results have been obtained by Bickford and Winton[12] by cooling the kidney to between 3 and 13° C. The effect upon the volume and composition of the urine is shown in the accompanying graph (Fig. 380). In spite of the fact that cooling reduces the blood flow to about one-half its normal value, the urine flow is greatly increased, showing that the reabsorption of water by the tubules has to a considerable extent been abolished. The similarity of the chloride concentration in the urine and plasma suggests that here also the urine produced is merely a filtrate. This is further borne out by the fact that creatinine, which is normally concentrated by the kidney, likewise approaches its plasma level.

What evidence have we that the forces acting across the glomerular membrane are adequate to account for filtration? It was first pointed out by Starling[133] that the osmotic pressure of the blood is determined by the plasma proteins. Since the plasma colloid osmotic pressure in the mammal is equal to 25-30 mm. of Hg, the formation of a protein-free fluid in the capsule requires that the hydrostatic pressure in the glomerular capillaries must at least exceed this figure. In addition, the pressure must be adequate to overcome the resistance to flow in the tubules. Winton estimates that the back pressure here is normally about 10 mm. of Hg. The filtration pressure is therefore equal to

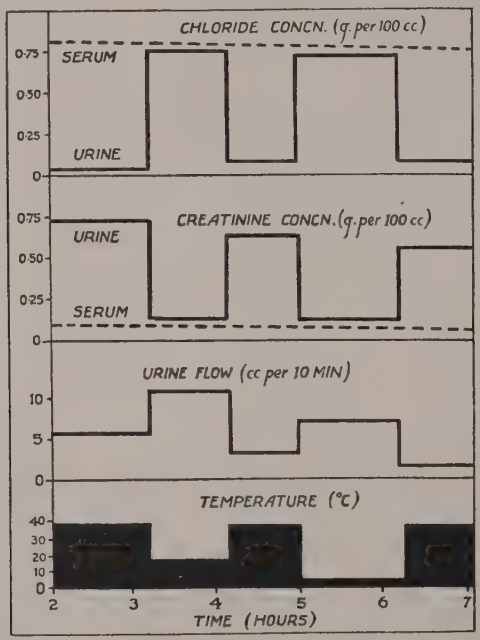


Fig. 380.—Diagram showing the influence of temperature on the isolated kidney of the dog. Cooling produces an increase of urine flow, and a change in its composition such that it has practically the same concentration of creatinine and chloride as serum. The effects are reversible. (After Bickford and Winton from Winton and Bayliss.[151])

the glomerular capillary pressure minus the colloid osmotic pressure and the pressure in the capsule, or, expressed in the form of an equation:

$$P_f = P_g - (P_{op} + P_c)$$

in which P_c is the pressure of the capsular fluid, P_{op} is the colloid osmotic pressure of the plasma, P_g is the glomerular capillary pressure, and P_f is the filtration pressure. By raising the ureteral pressure or lowering the blood pressure to a point where urine flow ceases (in which case $P_f = 0$), it is possible to arrive at a rough estimate of the glomerular capillary pressure and hence of the filtration pressure.

The ureteral pressure required to stop urine flow has been determined by a number of investigators. Figures as low as 10 and as high as 64 mm. of Hg

have been reported, but the usual value is 40 mm. of Hg. Adding to this the colloid osmotic pressure, which we may assume to be 25 mm. of Hg, it follows that the hydrostatic pressure in the glomerular capillaries must be about 65 mm. of Hg; in other words, somewhat more than half the arterial blood pressure. The ratio of the glomerular capillary pressure to the arterial pressure can also be determined by reducing the latter to the point where urine flow is suppressed. In the dog and the rabbit, Ustimowitsch[136] found this to occur at a pressure of 40 mm. of Hg. His observation has been confirmed by many others, notably Starling.[134] Winton,[149] however, raises the objection that a number of these experiments were carried out on kidneys secreting under the influence of large doses of diuretics. Even in the isolated kidney, in which reflex vasomotor effects are excluded, he finds that the urine flow usually stops when the arterial pressure is lowered to only 75 mm. of Hg. Nevertheless, if, for the sake of discussion, we assume that the minimum pressure is 50 mm. of Hg, we see again that the glomerular capillary pressure must stand at a little over half the arterial blood pressure. If this relationship holds when the

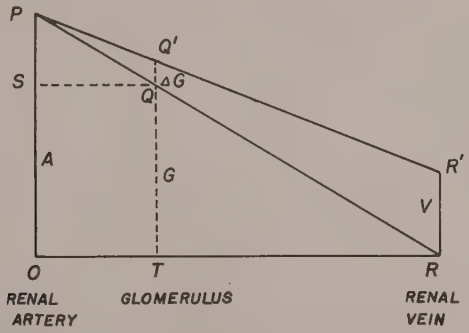


Fig. 381.—Diagram illustrating the relations between the arterial, glomerular, and venous pressures in the kidney. Ordinates, blood pressure. Abscissae, an irregular anatomical scale extending from the renal artery (*O*) to the renal vein (*R*); the intermediate points are defined by the condition that the blood pressure at any point lies on the straight line *PR*. (Redrawn from Winton.[149])

arterial pressure is normal, the glomerular capillary pressure is then between 60 and 70 mm. of Hg. In comparison with determinations of capillary pressure in other parts of the body, these figures are very high, but this is to be expected since the peripheral resistance in the kidney is principally in the efferent arterioles, whereas in the rest of the body the capillaries are placed beyond the peripheral resistance. Furthermore, our estimates agree quite well with Hayman's direct observations[62] on the frog, in which he found the glomerular pressure to be 54 per cent of the aortic pressure.

The glomerular capillary pressure in the heart-lung-kidney preparation of the dog has been calculated by Winton[149] from the equation:

$$\frac{\text{Glomerular pressure}}{\text{Arterial pressure}} = \frac{\text{Ureteral pressure}}{\text{Venous pressure}}$$

where the ureteral and venous pressures are so chosen that they cause the same reduction in the urine flow. Their values may be determined on a heart-lung-double-kidney preparation

if the urine flows from the two kidneys are initially the same. In one kidney the urine flow is then reduced by raising the venous pressure and the effect matched in the other kidney by raising the ureteral pressure.

The derivation of the equation and the assumptions on which it is based can best be understood from the diagram, Fig. 381. It is assumed that the pressure-fall from the renal artery O to the renal vein R follows the straight line PR. If the pressure in the renal artery remains the same when the venous pressure is raised from R to R′ (V), the pressures at various points in the system are then defined by the line PR′. That is to say, at any point in the system the increase in pressure caused by raising the venous pressure is proportional to the difference between the original pressure at that point and the arterial pressure. If T defines the position of the glomerulus on the horizontal scale OR, the glomerular pressure is initially QT. After raising the venous pressure it is Q′T. Since the triangles PQQ′ and PRR′ are similar, it follows that

$$\frac{QQ'}{RR'} = \frac{PQ}{PR}$$

Furthermore, by the similar triangles PQS and PRO it also follows that

$$\frac{PQ}{PR} = \frac{PS}{PO}$$

therefore,

$$\frac{QQ'}{RR'} = \frac{PS}{PO}$$

or

$$\frac{\Delta G}{V} = \frac{A - G}{A} \qquad (1)$$

where V is the increase in venous pressure, ΔG the increase in glomerular pressure, A the arterial pressure, and G the original glomerular pressure.

The rise in glomerular pressure ΔG is also related to the venous and ureteral pressures required to bring about the same decrease in urine flow.[148] This follows since an increase in the venous pressure has two effects which tend to alter the urine flow in opposite directions. The pressure in the vein is transmitted to the tubules and therefore raises the ureteral pressure; but the reduction in urine flow which would be produced by the latter is overcome to some extent by a concomitant increase in the glomerular pressure. Therefore the venous pressure V, which will cause the same reduction in urine flow as a given ureteral pressure U, must be higher than the latter by an amount which is equal to the increase in glomerular pressure. Thus,

$$\Delta G = V - U$$

Substituting for ΔG in (1) we have

$$\frac{V - U}{V} = \frac{A - G}{A}$$

or

$$\frac{U}{V} = \frac{G}{A}$$

The validity of this equation for calculating the glomerular pressure is indicated by the fact that under a constant arterial pressure the ratio of the ureteral and venous pressures required to cause the same reduction in urine flow is constant and independent of the absolute rate of flow at which the equivalent values of U and V are determined.

Utilizing this method of calculation, Winton[149] found the glomerular capillary pressure in the heart-lung-kidney preparation of the dog to be 65-75 per cent of the arterial pressure. With arterial pressures from 100 to 120 mm. Hg, the glomerular pressure ranged from 60 to 89 mm. Hg. We may conclude from these observations that the pressure-head in the glomerulus is adequate to overcome the colloid osmotic pressure of the plasma by a wide margin.

Recent evidence, however, suggests that there are other forces of considerable size which may oppose filtration. In this connection the reader should consult Winton's review on the *Physical Factors Involved in the Activities of the Mammalian Kidney.*[150] He points out that the diuresis produced by injection of saline is far greater (tenfold) than can be accounted for on the basis of the increase in the filtration pressure resulting from the dilution of the plasma proteins and the rise in blood pressure. Since saline has relatively little effect in the cooled kidney (tubular function suppressed), he is inclined to believe that its principal action is on the tubules. From the filtration surface in the glomerulus and the rate at which the filtrate is formed, it has been estimated that the pressure necessary to drive the fluid across the glomerular membrane is about 60 mm. Hg. It has also been estimated on theoretical grounds that the pressure required to drive the filtrate down the tubules may be equally large (25-80 mm. Hg); but judging from the height to which ureteral pressure may be raised without affecting the rate of urine flow, the back pressure in the tubules is only 10 mm. Hg. This back pressure is due to the intrarenal tension which is transmitted to the tubules. Since the kidney is enclosed in a nonelastic capsule, it is clear that swelling and shrinking of the renal tissue may have a considerable effect on the readiness with which urine escapes from the tubules, hence the anuria of certain types of edema and of the toxemias of pregnancy. As a last resort in these conditions, decapsulation of the kidney has been practiced, sometimes with beneficial results. The effect of changes in the intrarenal pressure also affords an explanation for the paradoxical increase in urine flow that results when a portion of the kidney substance is removed, or when one or two of the large branches of the renal artery are ligated.[150] Winton has demonstrated that the intrarenal pressure in this so-called "reduced kidney" is approximately one-half as great as in the intact kidney. It is evident from these observations that the intrarenal pressure must be regarded as one of the important factors which regulate urine flow both in health and in disease.

3. Tubular Function

If glomerular filtration is an established fact, it follows at once from the analyses of plasma and urine that the tubules must reabsorb at least some of the constituents (glucose and chloride) in the glomerular filtrate. Whether or not water is also reabsorbed is not so certain since the high urine concentration of such substances as creatinine and urea might equally well be explained by tubular excretion of these substances. The decision between reabsorption and excretion in the tubules can only be made when the volume of the glomerular filtrate is known. For the answer to these questions we must again turn first to experiments on the frog.

Tubular Function in the Amphibia.—Direct information on this question has been obtained by Richards and his co-workers from analysis of normal fluid collected at various points along the tubules and by observing the changes in the volume and composition of fluids perfused through isolated tubular segments.[110]

The technique presents certain difficulties because of the winding course of the tubules. The exact location of a puncture was determined after each experiment by injecting the tubule with India ink and immediately excising the entire nephron. In order to avoid the withdrawal

of fluid distal to the puncture, a small globule of mercury or oil colored with dye was injected into the lumen in such a way as to obstruct it distally. Sections of the tubules to be perfused were likewise isolated at both ends with globules of mercury. The perfusion fluid was then introduced into the lumen at one end of the segment and withdrawn at the other.

That the proximal tubule absorbs water is indicated by the fact that less fluid can be collected from the distal end of the proximal tubule than from the capsule. If Ringer's fluid is perfused through the lumen of the tubule at approximately the same rate as that provided by glomerular filtration, the amount collected is also less than the amount introduced. Furthermore, if glomerular filtration is abolished by blocking the capsule, it is impossible to obtain any fluid from the proximal tubule; consequently the proximal tubule does not excrete water under these conditions.

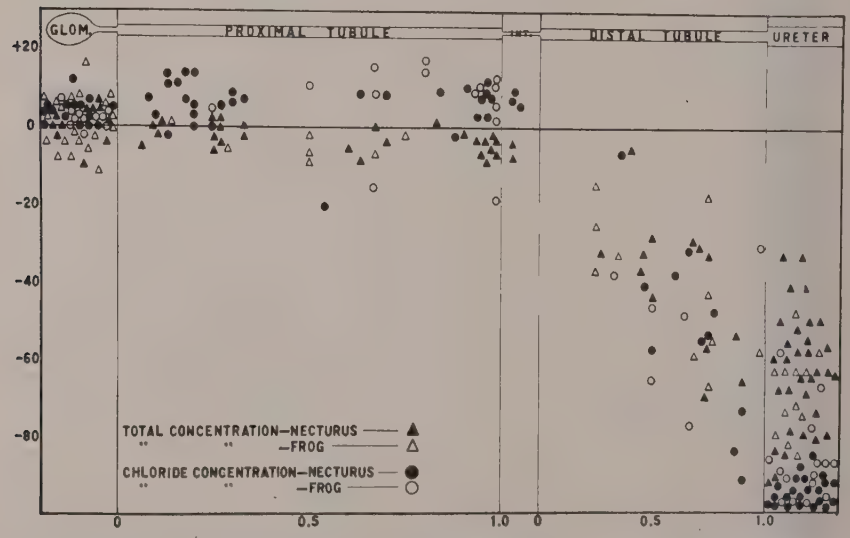


Fig. 382.—Chart showing differences between blood plasma and fluid collected from various levels of the renal tubules with respect to total concentration and Cl concentration. Sites of collection of tubule fluid can be identified by the points on the abscissa which represent fractions of the total length of the two chief segments of the tubule. Zero on the ordinate represents plasma. For chlorides, figures above and below represent percentage differences from plasma; for total concentration, they represent the micrometer scale divisions (each 5 μ) by which the 2 mm. capillary column of tubule fluid increased (+) or decreased (−) during forty-eight hours' equilibration against plasma. The representations of glomerular urine were taken from the previously published work of Walker[141] and Westfall, Findley and Richards.[147] (From Walker, Hudson, Findley and Richards.[148])

The results of chloride analyses on samples collected at various points along the tubule are shown in Fig. 382. This graph includes also determinations of the total molecular concentration. It will be seen that neither chloride nor total molecular concentration undergoes any significant change until the urine reaches the distal tubules; hence, the fluid which is absorbed in the proximal tubule must be essentially isotonic with the blood.

In contrast to the chloride, the glucose concentration in the glomerular filtrate falls rapidly after the fluid enters the proximal tubule (see Fig. 383). Perfusion of various parts of the tubules with Ringer's solution containing

glucose demonstrates that the reabsorption of glucose is limited to the proximal segment. In animals poisoned with phlorizin, on the other hand, the glucose concentration remains at or above the plasma level throughout the proximal tubule and appears in the ureter in high concentration. Consequently, the glycosuria produced by phlorizin is clearly due to an inhibition of reabsorption. Phlorizin does not, however, prevent the passive diffusion of some of the glucose back into the blood stream. This was shown by perfusing the proximal tubule of the mud puppy (Necturus) with Ringer's solution containing glucose in a concentration higher than that in the blood. The recovered fluid contained from 15 to 20 per cent less sugar than the perfusion fluid. In the same manner it was also shown that the tubules are partially permeable to the foreign sugar xylose.

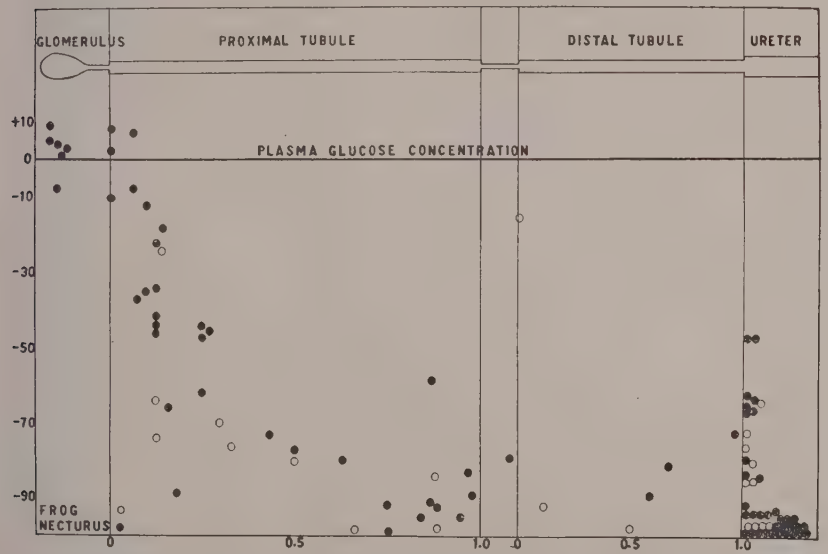


Fig. 383.—Chart showing differences in glucose concentration between blood plasma and fluid collected from various levels of the renal tubules of normal Necturi and frogs. Sites of collection of tubule fluid can be identified by the points on the abscissa which represent fractions of the total length of the two chief segments of the tubule. Zero on the ordinate represents plasma, figures above and below zero represent percentage differences from plasma. (From Walker and Hudson.[142])

Since the frog takes in large quantities of water through the skin, it must secrete a very dilute urine in order to preserve the normal concentration of salts in its body fluids. As shown in Fig. 382, this is accomplished by the reabsorption of sodium chloride in the distal tubule. This segment also reabsorbs sodium bicarbonate, for the urine suddenly changes from alkaline to acid in the last portion of the distal tubule (see Fig. 384). Furthermore, the distal segment is largely responsible for the reabsorption of water. This can be seen from the fact that after giving phlorizin, the concentration ratio (i.e., $\frac{\text{concentration in urine}}{\text{concentration in plasma}}$) of glucose in the tubular urine increases rapidly in

the distal tubule, finally reaching a value of 2.5. Richards estimates that only one-fifth of the total fluid reabsorbed is removed by the proximal tubules.

These experiments provide unquestionable evidence for tubular reabsorption and indicate furthermore that it consists of several independent and definitely localized processes. The next question to consider is whether or not tubular function is limited to reabsorption, and if not, to what extent tubular excretion contributes to the formation of urine.

Evidence for secretion in the tubules was brought forth by Nussbaum who took advantage of the opportunity presented by the double blood supply to the frog's kidney (see Fig. 378) for investigating tubular function independently. He found that although urine flow stops completely after ligation of the renal artery, it can be started afresh by injecting 1 to 1.5 ml. of 10 per

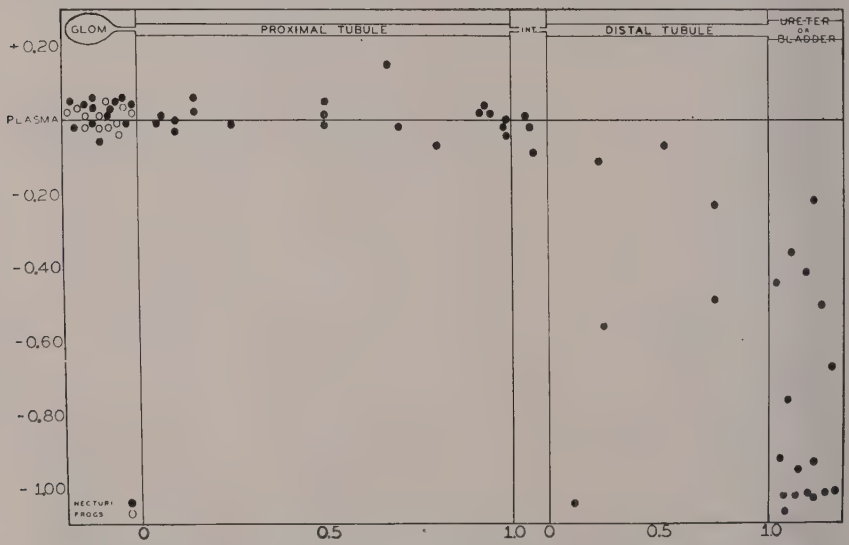


Fig. 384.—Reaction of glomerular urine in frogs and Necturi and of tubule urine in Necturi. Ordinates represent differences between fluid from the nephron and plasma as fractions of a pH unit; abscissae represent levels of the nephron from which fluid was collected. (Constructed from the data of Montgomery,[97] and of Montgomery and Pierce.[98]

cent urea into the anterior abdominal vein. The dye indigo carmine is also excreted under these circumstances. In 1906 the experiment was altered by Cullis to permit the perfusion of the arterial and venous systems separately. When attempts were made to repeat Nussbaum's observations with different techniques, many investigators questioned that ligation of the renal artery effectively occluded the glomerular circulation. Bensley and Steen[11] have pointed out that such observations were not valid because the experiments were done either without due regard for the precautions observed by Nussbaum or under conditions that were not analogous to those existing in the kidney after simply ligating the renal artery. By direct observation they found, as did Nussbaum, that the circulation through the glomeruli is completely stopped after the ligation.

On the other hand, as stated above (page 1099), the afferent arteries of the glomeruli sometimes give off branches directly to the tubules, and the efferent arteries may empty into either the renal-portal vein or the tubular capillaries, thus leaving open the possibility of some glomerular circulation. It was shown by Richards and Walker[109] that perfusion of the renal-portal system with Ringer's solution containing dye resulted in the appearance of dye in the glomerular capillaries. The possibility of an extra-renal collateral circulation was noted by Kempton,[72] who observed that the glomeruli of the posterior pole of a kidney in which the arteries were ligated could be perfused from the aorta. The source of this collateral circulation was from one of the two divisions of the normal arterial supply to the ureters. He found that when these collaterals from the ureter as well as the renal artery were ligated, no urine was excreted even after the injection of urea.

More convincing in the light of the clearance studies to be discussed presently, are the experiments of Marshall and Crane.[91] They have shown that the efficiency of the normal frog's kidney for excreting urea and phenol red is greater at low than at high plasma concentrations of these substances. That is to say, the kidney extracts a larger proportion of the dye or urea from the blood passing through the kidney when these substances are present in low concentrations. Furthermore, at high plasma levels the amount excreted is roughly the same regardless of the amount present in the plasma. If the amount excreted in the urine were derived solely from the glomerular filtrate, the rate of excretion would be directly proportional to the plasma concentration.

Analyses of tubular fluid in the frog show that urea is secreted by this species, and show furthermore that the secretion occurs mainly in the distal convoluted tubules.[110] In phlorizinized frogs, the maximum concentration ratio of glucose is about 2.5; whereas in the case of urea it may go as high as 20 or 30, showing that the high concentration of urea in the distal convoluted tubules and in the bladder urine cannot be explained simply by the reabsorption of water from the glomerular filtrate. Or to put it differently, the amount of urea excreted by the glomeruli is only a small fraction of the total amount excreted by the kidney. It is a mistake to assume from these experiments that tubular excretion of urea occurs in all animals, for even in the mud puppy, another amphibian, the concentration ratio of urea is no greater than that of glucose in the phlorizinized animal. Furthermore, we shall have occasion to note that in man urea is reabsorbed by the tubules.

Ammonia formation, demonstrated in the mammalian kidney by Benedict and Nash,[10] has recently been directly proved in the amphibian kidney by Walker.[140] Analyses of fluid collected at various points along the tubule show that ammonia appears first in the distal segment. Furthermore ammonia excretion continues when the kidneys are perfused with a fluid containing neither ammonia nor any known ammonia precursor. Since frog kidney extracts do not contain appreciable amounts of ammonia, there can be no doubt that it must be formed from some precursor, urea or amino acids, present in the tubule cells.

Tubular Function in the Aglomerular Kidney.*—The aglomerular fish provide an opportunity for the separate study of tubular function which is superior to that afforded by the Nussbaum frog preparation, if only because the obser-

*A detailed account of the functions of the aglomerular kidney may be found in the summaries by E. K. Marshall[90] and Homer Smith.[121]

vations can be made without anesthesia or surgical intervention. It was pointed out earlier that the tubule of the aglomerular kidney is the homologue of the proximal segment of the mammalian nephron. The similarity in function of other homologous structures wherever they occur among vertebrates suggests that the proximal segment of the mammalian tubule possesses, at least potentially, the same functional characteristics as the aglomerular tubule. Investigations of the renal function in the goosefish, the toadfish, the pipefish and the sea horse show that the aglomerular kidney is capable of excreting water, creatine, creatinine, urea, uric acid, magnesium sulfate, potassium and chloride. It can also excrete certain foreign substances, such as iodide, thiosulfate, sulfocyanide and the dyes, indigo carmine, neutral red and phenol red. The specialized character of aglomerular function is revealed in the above species by their inability to excrete ferricyanide, glucose, xylose, sucrose and inulin, all of which can be excreted by the glomerular kidneys of closely related marine forms. Increasing the blood sugar level to 400 or 500 mg. per cent or poisoning with phlorizin, both of which cause profuse glycosuria in glomerular kidneys, still leaves the urine from the aglomerular kidney sugar-free. That the aglomerular kidney is a pure secretory organ is futher demonstrated by the fact that the maximum secretion pressure may exceed the dorsal aortic pressure, whereas in the glomerular kidney this is always lower than the blood pressure. Consequently, urine formation in the aglomerular tubule is accomplished by secretion, and it will be seen that this function is to a certain extent retained in the mammalian tubule.

Tubular Function in the Mammalian Kidney.—From the similarity in structure of the mammalian and the amphibian nephrons, it is reasonable to expect that urine formation in both involves approximately the same processes. We have sufficient evidence to be certain that the analogy holds so far as the glomerular function is concerned. But, to assume that the pattern of tubular function in the frog would be repeated in the mammal in every detail is, to say the least, hazardous, for we have seen that even in the mud puppy, a close relative of the frog, there is a marked difference with respect to the excretion of urea. Furthermore, the mammalian tubule shows, aside from its greater length and larger number of convolutions, an important structural difference in that it possesses a thin segment, the appearance of which in the animal scale coincides with the ability of the kidney to excrete hypertonic urine.

Granted that the glomerulus acts as a simple ultrafilter, it follows from the arguments put forth by Cushny in support of the modern theory that the tubules reabsorb at least those diffusible constituents in the plasma which are absent from the bladder urine. We have seen that this applies specifically to glucose and chloride. That the tubules also reabsorb water is demonstrated by the experiments of Starling and Verney[135] and of Bickford and Winton,[12] which were described in connection with glomerular filtration. Suppression of tubular function, either with cyanide or by cooling, results in the formation of a larger amount of more dilute urine. The effect of cooling constitutes particularly impressive evidence for reabsorption inasmuch as the increase in rate of urine flow occurs in spite of a large decrease in renal blood flow. In addition, the change is reversible, showing that the glomerular membrane is not damaged by lowering the temperature.

Convincing evidence for tubular excretion in the mammal has been obtained from experiments with phenol red. It will be remembered that this dye has a tendency to combine with the plasma proteins; dialysis through semipermeable membranes shows that only 25 to 30 per cent is freely diffusible. Marshall and Vickers[92] calculated that in the dog the amount of diffusible phenol red brought to the kidney is entirely inadequate to account for the rate of excretion of this substance, even if it is assumed that the renal blood flow is maximal and that all the plasma is filtered off in the glomerulus. This conclusion was fully confirmed by Sheehan's experiments[117] on the explanted kidney of the dog, in which the phenol red extraction ratio was determined from the difference in dye content of arterial blood and renal vein blood and from the rate of phenol red excretion. Sheehan and Southworth[118] have demonstrated that this dye is also excreted by the tubules in the rabbit.

4. Analysis of Renal Function From Plasma Clearances

During recent years, great progress has been made in the study of renal function by applying the concept of *plasma clearance*. This term may be defined as the volume of plasma cleared of a given substance per minute by the kidney or, more correctly, the volume of plasma which would be required to provide the amount of the substance excreted per minute. It is calculated from the simultaneous plasma and urine concentrations of the substance and from the volume of urine formed per minute. If P is the plasma concentration of the substance, U its urine concentration and V the rate of urine flow in milliliters per minute, the plasma clearance may be expressed as follows:

$$\text{Plasma clearance in ml. per min.} = \frac{U \times V}{P}$$

In other words, the plasma clearance of any substance is equal to its concentration ratio $\frac{U}{P}$ multiplied by the rate of urine flow.

The implications of this concept become clear if we return for a moment to consider Cushny's theory. According to Cushny, all substances present in the urine are derived from the glomerular filtrate; furthermore, certain substances which he called no-threshold substances are not reabsorbed in the tubules. If this hypothesis be accepted, then the plasma clearance of a true no-threshold substance is equal to the glomerular filtration rate, for if the substance is neither reabsorbed nor secreted by the tubules, the amount filtered through the glomerulus is equal to the amount recovered in the urine. Therefore, the quantity $U \times V$ must be equal to plasma concentration of the substance multiplied by the volume of glomerular filtrate in which it was contained.

The possibilities that develop from this reasoning are not difficult to visualize. If the glomerular filtration rate can be measured, we are at once in a position to evaluate quantitatively the part played by the glomeruli and the tubules in the excretion of any given constituent in the urine. Thus if the plasma clearance of a substance is greater than the glomerular filtration rate, we have evidence of tubular excretion; and if its clearance is less than the glomerular filtration rate, we can say that the substance is being reabsorbed. The fundamental problem is to find a substance, the clearance of which is equal to the glomerular filtration rate under all conditions. The search, led

chiefly by Homer Smith and his collaborators, constitutes one of the most illuminating chapters in renal physiology. The reader is urged to consult Smith's recent publications for a detailed account of this important subject.[129, 131]

A substance which is to be used for measuring glomerular filtration rate must satisfy a number of requirements. (1) It must diffuse freely through the glomerulus and therefore must not combine with the plasma proteins to which the glomerulus is impermeable. (2) It must not be excreted by the tubules. (3) It must not be reabsorbed in the tubules. (4) It must be physiologically inert, not only in the sense of being nontoxic, but especially with respect to its effect on renal function either directly or indirectly. (5) It must be a substance which can be determined accurately in plasma and urine.

Method of Determining Plasma Clearance.—If the substance under consideration is not a normal constituent of the plasma, or if its plasma level is too low to be accurately determined, it must be administered in suitable amounts and preferably at a uniform rate in order to maintain its plasma concentration at or near the same level during the period of the test. This can usually be accomplished most readily by giving a continuous intravenous injection preceded by a large priming dose. Blood and urine samples are collected at frequent intervals, particular care being taken to collect all the urine excreted during each period by washing out the bladder with a known volume of saline and expelling the last traces of fluid by insufflation with air. The volume of each urine sample is obtained by subtracting the volume of saline used for washing. In spite of these precautions some error may arise from the fact that an undetermined though probably small volume of urine remains in the tubules and the ureters. The results obtained from analysis of the plasma samples are then plotted against time and the plasma concentration at the midpoint of each period determined by interpolation of the time-concentration curve.

The measurement of glomerular filtration rate in man was first attempted by Rehberg.[107] He chose creatinine for this purpose, since among the normal urinary constituents it displays one of the highest concentration ratios (about 100), a fact which, according to Cushny's theory, would indicate that it is not reabsorbed by the tubules. Since Cushny's theory also denies the existence of tubular excretion, Rehberg assumed that the plasma clearance of creatinine is equal to the glomerular filtration rate. But, when it was subsequently shown that in man creatinine is actually excreted by the tubules, it became evident that Rehberg's results were founded on an insecure hypothesis.

In the search for substances not likely to be secreted by the mammalian tubule, valuable leads were obtained from the study of renal function in the aglomerular fish. It will be remembered that glycosuria cannot be induced in the aglomerular kidney either by raising the plasma concentration of glucose or by poisoning with phlorizin. Since phlorizin inhibits tubular reabsorption of glucose in the glomerular kidney, the glucose clearance in the phlorizinized animal should be equal to the glomerular filtration rate, and thus constitute a useful standard to test other substances for use in measuring the glomerular filtration rate in normal animals. Among the first substances tested were xylose, sucrose and raffinose. Tubular excretion of these foreign sugars by the mammalian kidney seemed improbable since it was found that they are not excreted by the aglomerular kidney. Tubular reabsorption was also unlikely since they were known to be eliminated rapidly by the normal mammalian kidney. These suppositions were confirmed by the fact that in the phlorizinized dog, the clearances of all three sugars are the same as that of glucose. Furthermore, their clearances are independent of their plasma concentrations. This fact also indicates that the tubules do not reabsorb or excrete these sugars, for in either case it is very improbable that active tubular processes would be closely adjusted to the plasma concentration. More recent work, however, has shown that their plasma clearances in the normal animal are not identical with the glomerular filtration rate because all three are partly reabsorbed in the tubules. According to Homer Smith, this reabsorption is associated in some way with the reabsorption of glucose and does not occur when the latter is prevented by phlorizin.

The Plasma Clearance of Inulin.—Recent evidence obtained independently by Richards and by Smith and their respective coworkers now points to inulin

as being a substance which under all conditions has a plasma clearance that is identical with the glomerular filtration rate.

Inulin is a polysaccharide with a molecular weight of about 5,000. It is subject to satisfactory chemical analysis and when injected intravenously is not metabolized but excreted quantitatively by the kidney. It produces no untoward symptoms in human subjects, and, so far as is known, has no effect upon the circulation or the renal function. That inulin is freely filtrable is shown by the fact that in the frog its concentration in the glomerular fluid is the same as in the plasma. It also diffuses freely through collodion membranes impermeable to the plasma proteins. It is not excreted by the aglomerular kidney, but is eliminated rapidly by the glomerular kidney. As in the case of xylose, the clearance is independent of its plasma concentration. Furthermore, in view of its large molecular weight, inulin does not, in all probability, diffuse out of the tubules. This is indicated by the fact that in the normal dog and in man (see Fig. 385) the inulin clearance is greater by about 25 per cent than the simultaneous clearances of xylose and sucrose, both of which are to some extent reabsorbed by the tubules. After phlorizin, the simultaneous clearances of xylose, sucrose, glucose and creatinine are identical with that of inulin. The agreement under these conditions is brought about by a large rise in the glucose clearance (active tubular reabsorption abolished), a smaller increase in the xylose and sucrose clearances (partial reabsorption abolished), and a drop in the creatinine clearance* (tubular excretion abolished). The clearance of inulin itself is unaffected by poisoning with phlorizin. As may be seen from Fig. 385, Smith maintains that the clearances of the polyhydric alcohols, sorbitol and mannitol, are identical with that of inulin.

These facts constitute strong evidence that the inulin clearance in the phlorizinized animal is equal to the glomerular filtration rate, for it is difficult to believe that tubular excretion and reabsorption would affect all substances in the same way. Furthermore, since phlorizin has no effect upon the inulin clearance, it follows that the latter must be identical with the glomerular filtration rate in the normal kidney. Thus by comparing the simultaneously determined clearances of other substances with that of inulin, it is possible to estimate the extent to which various urinary constituents and foreign substances are excreted or reabsorbed by the tubules.

In man the ratio, $\frac{\text{creatinine clearance}}{\text{inulin clearance}}$ is ordinarily about 1.40. Consequently, tubular excretion accounts for about 30 per cent of the total creatinine normally removed by the kidney; but if the plasma level is raised, this fraction excreted by the tubules is smaller (see Fig. 386). It has been suggested that the kidney distinguishes between endogenous and exogenous creatinine, the former being secreted by the tubules and the latter being filtered through the glomerulus. The question is still unsettled because the determination of creatinine in plasma may not be sufficiently specific to exclude other substances. In the dog, however, the creatinine and inulin clearances are identical, an indication that in this species creatinine is excreted by glomerular filtration only.

The manner in which urea and phenol red are handled by the kidney in man is of especial practical interest, as these substances have been used extensively for kidney function tests. Referring to Figs. 385 and 386, it may be seen that the normal urea/inulin clearance ratio is about 0.6, showing that approximately two-fifths of the urea cleared by the glomerulus is reabsorbed in the tubules. It is generally believed that this is due merely to passive diffusion, an explanation which Shannon[116] finds inadequate. Thus, if the standard urea clearance test yields a low value in renal disease, it might indicate either a diminished glomerular filtration rate or an increased permeability of

*This refers only to man. In the dog creatinine is not removed by tubular excretion.

the tubules. According to results obtained on the explanted kidney by Van Slyke, Rhoads, Hiller and Alving,[137] tubular permeability to urea may be temporarily increased even by physiological disturbances. The normal phenol red/inulin clearance ratios (compare their clearances in Fig. 386) show that in

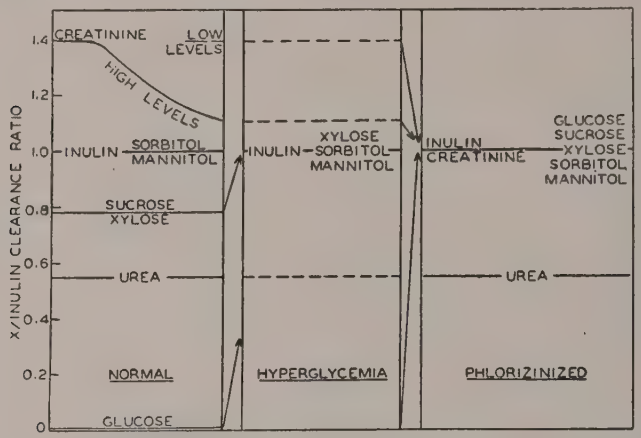


Fig. 385.—Diagrammatic summary of the present evidence, based on clearance ratios, indicating that the inulin clearance is at the level of glomerular filtration in man. (H. W. Smith.[129])

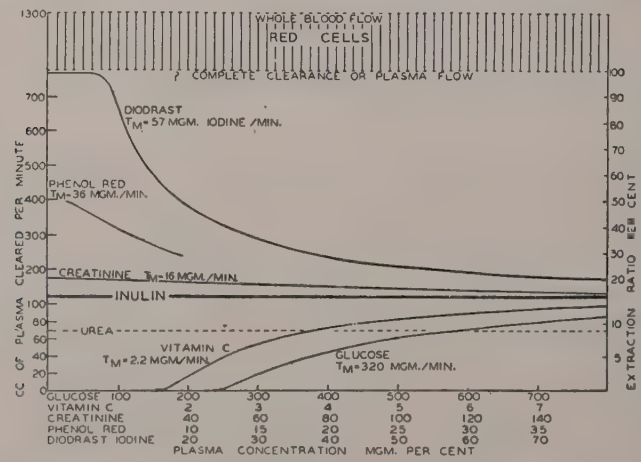

WHOLE BLOOD FLOW
RED CELLS
? COMPLETE CLEARANCE OR PLASMA FLOW
DIODRAST
T_M = 57 MGM. IODINE /MIN.
PHENOL RED
T_M = 36 MGM./MIN.
CREATININE T_M = 16 MGM./MIN.
INULIN
UREA
VITAMIN C
T_M = 2.2 MGM/MIN.
GLUCOSE
T_M = 320 MGM./MIN.
CC OF PLASMA CLEARED PER MINUTE
EXTRACTION RATIO PER CENT
GLUCOSE 100 200 300 400 500 600 700
VITAMIN C 2 3 4 5 6 7
CREATININE 40 60 80 100 120 140
PHENOL RED 10 15 20 25 30 35
DIODRAST IODINE 20 30 40 50 60 70
PLASMA CONCENTRATION MGM. PER CENT

Fig. 386.—Diagrammatic summary of excretion of various types of compounds by the human kidney. (From H. W. Smith.[129])

man as well as in the dog the kidney removes phenol red chiefly by tubular excretion. Thus in comparison with the normal, the rate at which the diseased kidney excretes a standard amount of phenol red would be an index of the secretory capacity of the tubules, but not accurately so since some dye is also excreted by glomerular filtration. As the plasma level of phenol red is in-

creased, the tubular excretion reaches a maximum value. The determination of this maximum capacity of the kidneys to excrete the dye is proportional to the so-called "tubular excretory mass" and constitutes a quantitative method of estimating the extent of tubular damage.[116]

Glomerular Filtration Rate and Urine Flow.—It may be seen from Fig. 386 that the inulin clearance in man is about 120 ml. per minute. Since the urine flow is usually about 1 ml. per minute or 1.5 liters per day, it follows that tubular reabsorption goes on at the rate of 119 ml. per minute. Thus in twenty-four hours the kidneys filter about 170 liters of fluid and reabsorb 168 or 169 liters, containing 1,000 grams of sodium chloride, 360 grams of sodium bicarbonate and 170 grams of glucose. Since this is accomplished by some 2,000,000 secretory units, the rate of filtration in each glomerulus is about 0.001 c.mm. per second. With a filtration pressure of at least 50 mm. of Hg, the formation of this quantity of fluid does not seem to be an insurmountable task.

The glomerular filtration rate as measured by inulin clearance is remarkably constant in man. It can be altered by changes in the blood pressure and by vasomotor reflexes; but hydration or dehydration, unless driven to the extreme, appears to have little effect. Normally, therefore, the urine volume must be determined by the rate of tubular reabsorption. Even this process is subject to variation within relatively narrow limits. Inasmuch as the maximum urine flow does not exceed 20 ml. per minute, i.e., less than one-fifth of the glomerular filtration rate, it would seem that the reabsorption of at least four-fifths of the glomerular filtrate is a fixed process under all conditions, leaving the rest to be reabsorbed or not, in accordance with the demands for water conservation.

The constancy of the glomerular filtration rate is rather surprising in view of the fact that the arrangement of the blood vessels in the renal corpuscle is such that one would expect large fluctuations in the pressure and flow of blood in the glomerulus. But it may well be that reflex mechanisms exist which tend to keep them constant. This, however, is not in accord with direct observations on the frog in which the glomerular filtration rate varies greatly and the glomerular circulation shows a characteristic spontaneous intermittance. Under normal circumstances, only a small proportion of the glomeruli in the frog's kidney is active at one time, the activity shifting from one to the other. Also in the individual glomeruli, the circulation may change spontaneously, involving first one capillary loop, then another, or suddenly continuing through all. Thus, the filtration surface may be very different from time to time. It is decreased by hemorrhage or by application of adrenalin, and increased by the intravenous injection of saline or blood and by diuretics, such as urea and glucose. Variations such as these in the distribution of blood in the kidney should have pronounced effect on the rate of urine secretion, for if we consider ten individual secretory units in which the filtration surface may be altered tenfold by opening or closing the capillary loops, it is apparent that the quantity of fluid filtered must vary accordingly. Furthermore, given the same number of patent glomerular capillaries, and hence the same volume of filtrate, the final composition of the urine will obviously depend upon whether the filtrate is poured into a few tubules or distributed among a larger number.

Measurement of Renal Blood Flow With the Clearance Method.—From Fig. 386 which provides an instructive summary of the manner in which various

substances are excreted by the kidney, it may be seen that at low plasma levels the clearances range from zero, for glucose and vitamin C, to 400 ml. per minute for phenol red and to more than 700 ml. per minute for diodrast. The plasma is obviously cleared of diodrast with remarkable efficiency. The diagram furthermore shows that in the case of this substance the maximum clearance is reached at a plasma concentration of about 10 mg. per cent. What limits the increase in clearance with further reduction in the plasma level of diodrast? The answer appears to be that the upper limit of clearance values has been reached—that the kidneys are excreting all of the diodrast brought to them by the blood (100 per cent extraction). Under these circumstances the clearance is therefore equal to the milliliters of plasma flowing through the kidneys per minute, and if the hematocrit is known, one may calculate the total renal blood flow. Comparison of the diodrast concentrations in blood taken from the renal artery and vein shows that the extraction is practically complete. Other evidence of less direct nature also justifies the assumption that the diodrast clearance is essentially equivalent to the plasma flow.[129, 132] It should be added that Smith and his associates have employed the diodrast clearance method in a most fruitful study of the renal circulation in man.[130]

C. REGULATION OF RENAL FUNCTION

From the preceding discussion of the mechanism of urine formation, it may be seen that the renal function as a whole is subject to a multiplicity of influences. Principal among them are those changes in the general circulation which affect the pressure and flow of blood through the renal artery,[130] vascular adjustments within the kidney itself, and changes in the ureteral and intrarenal pressures, which in turn are influenced by the volume and pressure of the blood in the kidney. Thus, hemorrhage, and the vasomotor disturbances accompanying excitement, digestion, muscular activity, etc., may have marked effects on urine flow. The intra-abdominal pressure must also be considered. One is tempted to speculate on its possible connection with the sluggish response of the kidney to water ingestion during pregnancy.

All these circulatory disturbances and mechanical pressures influence kidney function by virtue of their effects on the glomerular filtration rate. It is doubtful whether normally they serve to integrate renal excretion with the bodily requirements, for the glomerulus as a filter does not act specifically to maintain the composition of the blood. The fine adjustment of renal function to disturbances in the latter is attributable to selective processes in the tubules.

It is hardly necessary to point out that the kidney is remarkably versatile and discriminating in its activity. For example, it is a matter of common experience that the excretion or retention of ingested water depends upon the state of hydration of the body. Yet whatever happens to the water, the concentration of the blood is hardly affected. We have seen that in the case of glucose, a sharp distinction is made by the kidney on the basis of the plasma concentration of this substance. Although the threshold for sodium chloride is less clearly defined, it is excreted or rejected in accordance with the bodily supply. Normally the intake of salt is in excess of the requirements, with the result that a considerable amount is usually excreted. But if salt has been lost in sweat or if the diet is deficient in sodium chloride, the amount in the urine

dwindles to very low levels. The kidney also plays an essential part in the maintenance of the hydrogen ion concentration of the blood. If there is a slight preponderance of anions in the body fluids, the urine becomes acid out of all proportion to the change in the blood. Considerable base is then conserved, since in an acid medium the urinary phosphate is excreted largely as a monobasic rather than as a dibasic salt. Furthermore, under these conditions the kidney may form larger amounts of ammonia with which the excess acid may be excreted without its usual complement of fixed base. On the other hand, when the body fluids contain an excess of fixed base, the formation of alkaline urine permits the excretion of phosphate as a dibasic salt. Also bicarbonate now supplants the chloride. Both processes result in the conservation of chloride, which would otherwise be required for the excretion of fixed base.[37] Aside from these and other essential constituents of the plasma, the kidney must also cope with a great variety of foreign substances and waste products which are presented for excretion in variable amounts. In all instances retention or excretion is determined by tubular activity. The glomerulus makes no distinction except on the basis of molecular weight; only the proteins and substances which are made nondiffusible by combination with them are held back by this part of the secretory unit.

Water Diuresis.—The ingestion of a moderate amount of water (1.0-1.5 liters) usually has a marked diuretic effect. The increase in urine flow is noticeable within twenty to thirty minutes; it rises to a maximum in one to two hours and subsides to the previous level in three to five hours. The volume of fluid excreted during this period is normally equal to or slightly greater than the volume ingested. The urine is pale in color and its specific gravity low, 1.002 as compared with the normal value of 1.020, showing that the excretion of water is not accompanied by an increase in the excretion of solutes. The response in this respect, however, is conditioned somewhat by the supply of salt in the body.

The well-recognized sensitivity of the kidney to changes in the composition of the blood led many investigators to seek the cause of water diuresis in blood dilution.[57, 111, 122] As a result, the literature now contains abundant data dealing with the effect of water ingestion on the water content of the blood as measured by the concentration of hemoglobin, plasma proteins, total solids and chloride, and by the conductivity of the serum. A survey of all these data shows that although hemoglobin and plasma proteins are usually diluted slightly, this change is by no means essential for the occurrence of diuresis. Using the method for measuring plasma volume described in Chapter LXXVIII (see Figs. 367 and 372), the author and his collaborators have found that water diuresis may occur without evidence of dilution of the dye injected prior to the experiment. This constitutes definite evidence that there is no increase in the total plasma volume, a fact which cannot be concluded from the hemoglobin or plasma protein determinations mentioned above, since the amount of these substances circulating in the blood may itself change.

The electrolytes are the only constituents of the blood which appear to be consistently affected by the ingestion of water. Careful determinations of total osmotic pressure of serum by Baldes and Smirk[5] (Hall's vapor pressure method) show that there is a decrease of between 1.5 and 2.75 per cent in the electrolyte concentration within thirty minutes after the ingestion of one liter

of water. It will be seen that this is precisely the dilution one would expect if the ingested fluid were distributed equally through all the water in the body (about 45 liters). Furthermore, the time (thirty minutes) required for the dilution to take place is a measure of the rate at which the water is absorbed from the gut. The rate of absorption has been determined with an attractively simple method devised by Smirk.[121] By placing the abdomen or the legs of the subject on weighing scales in a suitable manner, he found that after one liter of water had been ingested, the weight of the abdomen gradually decreased, whereas the weight of the legs increased. The change was complete within twenty-five to fifty-five minutes. The percentage increase in leg weight (1.15) corresponded closely with the dose of water (1.3 per cent of the body weight), again indicating that the fluid is distributed equally through all the water in the body. The change in electrolyte concentration does not, however, affect the kidney directly, for it has been found by Rioch[111] and confirmed by many others that there is a lag of some fifteen to twenty minutes in the diuresis. If the blood is diluted by injecting water intravenously the same lag occurs.[101] Furthermore, the absolute level of the plasma electrolyte appears to be of minor significance, as water diuresis may occur either when the plasma electrolyte concentration has been lowered by salt-deficient diets or sweating, or when it has been raised by increasing the salt intake.

It has long been suspected that renal excretion of water may be controlled by a hormone from the posterior lobe of the pituitary gland. The hormone was first thought to have a diuretic action when Magnus and Schäfer[87] found, many years ago, that extracts of the posterior lobe cause increased flow of urine in anesthetized animals. This, however, is attributable to a temporary circulatory disturbance and does not represent the specific renal effect of pituitrin which, on the contrary, is antidiuretic. The latter is demonstrated by the fact that pituitrin retards water diuresis for several hours in the normal unanesthetized animal, reduces the polyuria in diabetes insipidus and diminishes the urine flow in the isolated heart-lung-kidney preparation when added in minute amounts to the blood perfused through the kidney. It should be pointed out that pituitrin does not reduce the diuresis caused by salt or urea. Its action is limited to the urine water not required for the excretion of solutes.[3]

These observations and the experience that the polyuria of diabetes insipidus is associated with lesions in the vicinity of the hypophysis indicate that the renal output of water is regulated by the antidiuretic hormone from the posterior lobe. Seemingly in conflict with this view are the facts that complete removal of the pituitary gland does not consistently result in polyuria, that diabetes insipidus can be produced experimentally by hypothalamic puncture, and that the occurrence of the disease is not invariably associated with tumors that involve the posterior lobe directly. It might be assumed that the hormone acts upon nerve centers in the base of the brain and that in the absence of the pituitary these can still regulate the water output. But actually these possibilities are out of the question, since the antidiuretic effect of pituitrin is exerted upon the denervated or isolated perfused kidney as well as on the normally innervated kidney. Furthermore, denervation of the kidney neither abolishes polyuria nor interferes with its development in experimental diabetes insipidus. The recent investigations of Ranson and his co-workers[31, 32, 34, 35, 69, 70] have thrown much light on this confusing problem. For a summary of the

literature the reader should consult their reports. Using the Horsley-Clarke stereotaxic instrument, they were able to approach the hypothalamic region from above and to make sharply localized lesions in the hypothalamic nuclei and in the fiber tracts between these and the pituitary, without disturbing the pituitary itself. In cats and monkeys they found that polyuria was consistently produced by destruction bilaterally of the supraoptic nuclei, or of the fiber tracts leading from these to the posterior lobe. In animals thus treated the posterior lobe atrophies, and extracts made from four such glands in the cat showed little or no antidiuretic effect. The reports that polyuria is not produced after extirpation of the entire pituitary seem to be explained by incomplete removal of posterior lobe tissue lying along the stalk, and not by the claim recently put forth that the anterior lobe secretes a diuretic hormone. The diuretic effect of anterior lobe extracts appears to be related to changes in metabolism since it is said to depend upon the thyroid.

The view now generally accepted is that both normal water diuresis and the polyuria of diabetes insipidus are the result of a decrease in the amount of the antidiuretic hormone supplied to the kidney. That the hormone acts directly upon this organ is attested by the experiments on the isolated and denervated kidney, mentioned above. The antidiuretic effect is brought about by increased reabsorption in the thin segment of the tubule for, as Burgess, Harvey and Marshall[16] have shown, pituitrin does not retard water excretion in lower animals in which the thin segment is lacking (see Fig. 377). The existence of hormonal control of water excretion is indicated by the experiments of Klisiecki, Pickford, Rothschild and Verney[73] on dogs with exteriorized ureters and one kidney denervated. In this preparation the delay between increased water load of the body and diuresis is identical for both kidneys. Inhibition of water diuresis by afferent stimulation also affects the normal and denervated kidney equally. In this case too, the effect is not immediate but occurs after ten to fifteen minutes. It has also been reported that the injection of blood from a normal animal retards water diuresis, whereas no antidiuretic effect is observed after injection of blood obtained from animals during diuresis.[131] Gilman and Goodman[43] report that the antidiuretic hormone is excreted in the urine and that the amount excreted is related to the need of the organism for water conservation. They found that urine from dehydrated rats contains large amounts of antidiuretic substance which is entirely absent from the urine collected during water diuresis or after the animals have been hypophysectomized.

Diuretics.—The consideration of diuretics belongs more particularly to the province of pharmacology, since many of the substances included in this category may be classed as drugs. It is sufficient here merely to mention some of the ways in which these substances may promote the flow of urine.

By the term *diuretic* is usually meant a substance which, if injected in small amounts, increases the urine flow by specific renal effects. In many instances, however, this definition appears to be incorrect, for the analysis of the action of a number of diuretics shows that they exert their influence in part through the circulation and the central nervous system. The diuresis from caffeine, for example, may be the result of a diminished output of antidiuretic hormone, since caffeine is known to have a marked action on the nervous system. Within the kidney itself, diuretics may act by stimulating the glomerular circulation, as is the case with caffeine, or by hindering reabsorption in the tubules. The latter can be most simply explained as an osmotic effect resulting from the inability of the diuretics to diffuse through the tubular epithelium. Among the substances that behave in this manner are sulfate,

urea and sucrose. The diuresis which follows the ingestion of acidifying salts (e.g., NH_4Cl, and $CaCl_2$) is presumably the result of the disturbance in the acid-base equilibrium of the blood.

The Function of the Renal Nerves.—The presence of nerve fibers in and among the tubule cells suggests that there may be some specific neural control of tubular excretion and reabsorption, especially since the activities of true secretory cells in many other parts of the body are known to be regulated by the nervous system. According to the best authorities, however, the evidence which seems to indicate the existence of specific secretory nerve fibers in the kidney can be explained on the basis of changes brought about by the vasomotor nerves or by complicating experimental factors, such as anesthesia. We have already noted that the denervated kidney does not reveal any deficiencies in its finer adjustments to external influences or to the composition of the blood. For the present, then, it must be assumed that the action of the renal nerves on urine formation is limited to their effect on the pressure and flow of blood through the kidney.

CHAPTER LXXXIII

THE URINARY BLADDER

By Walter S. Root

The urinary bladder is an organ designed for the storage of fluid. Urine, formed in the kidney, is propelled down the ureters by rhythmic peristaltic waves and enters the bladder in spurts. Here, it is temporarily stored and periodically voided. The ureters, which traverse the bladder wall obliquely, are compressed easily by contractions of the detrusor muscle. This prevents reflux of urine as the intravesical pressure rises.

The bladder muscle exhibits two types of activity: sustained contraction or tonus, and intermittent contractions. The act of micturition demands the coordination of these common smooth muscle responses with sphincter activity, in which the intervention of the central nervous system is essential.

The Nervous Control of the Bladder

The Innervation of the Bladder and Urethra.—Most experimental investigations of bladder function have been carried out upon the cat. In this animal, the smooth muscle of the vesicle derives its sympathetic innervation from the lumbar splanchnic nerves which leave the spinal cord between the second and fourth lumbar segments (Fig. 387). Passing through the corresponding ganglia of the abdominal sympathetic chain, the majority of these fibers enter into synaptic relation with a second neuron in the inferior mesenteric ganglia. The postganglionic fibers run downward in the hypogastric nerves to supply the body and neck of the bladder. Parasympathetic fibers from the first three sacral segments unite on each side to form the pelvic nerve (nervus erigens). Sympathetic and parasympathetic nerves mingle in the hypogastric (pelvic) and vesical plexuses. The short postganglionic parasympathetic fibers, arising in the vesical ganglia, pass to the body and neck of the bladder. In the cat, the entire bladder neck serves as the internal sphincter. The striated compressor urethrae muscle, constituting the external sphincter, is innervated by the pudendal (pudic) nerves. It is commonly stated that the pudendal nerves emerge between the first and fourth sacral segments, although some authors[9] restrict their origin to the first two sacral roots.

Stimulation Experiments.—Attempts to study the function of the nerves supplying the bladder by stimulation experiments have yielded equivocal results. Indeed, it has been reported[11] that the responses depend upon the nature and the depth of the anesthesia, as well as upon the tonus of the detrusor muscle. More conclusive data have been obtained by the investigation of bladder reflexes in which it is possible to employ more natural stimuli.

Bladder Reflexes.—Barrington, who has studied the control of the feline bladder in considerable detail, distinguishes six bladder reflexes[1, 2, 3, 4] (see Table CXXIV). The following discussion is based upon his observations.

When the bladder of a lightly anesthetized[1] or a decerebrated cat[2] is distended with a moderate quantity of fluid, there is a transient rise in intra-

vesical pressure which decreases as the organ adapts its capacity to the changes in volume. As successive volumes of fluid are introduced, the curve of intravesical pressure shows a gradual steplike ascent. At a certain point in vesical filling, the detrusor muscle contracts, the bladder neck and the compressor urethrae muscle relax, and the contents of the bladder are expelled. Since changes in bladder capacity require some little time, the reflex may be elicited at

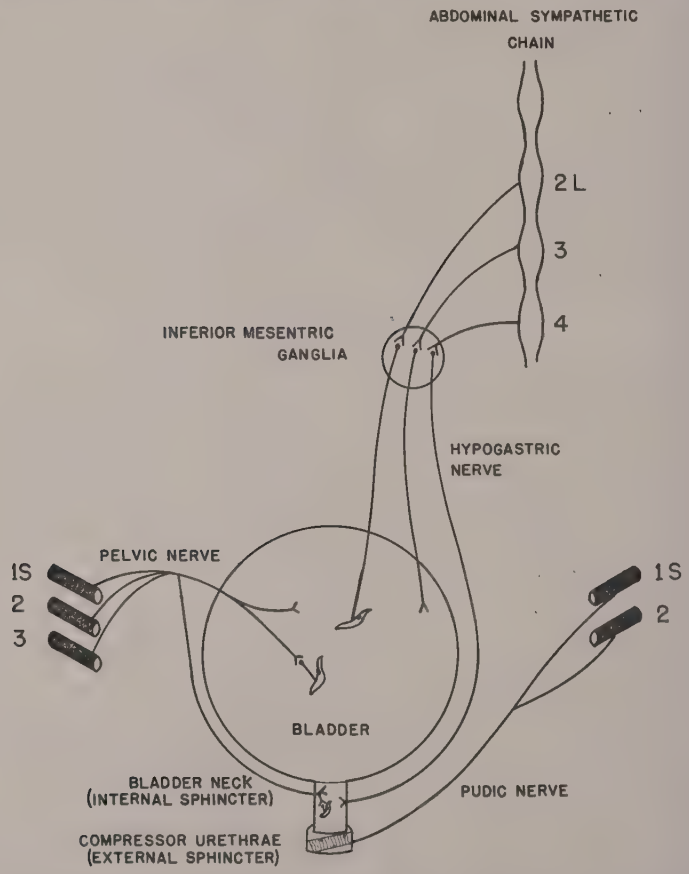


Fig. 387.—Diagrammatic representation of the innervation of the urinary bladder in the cat. (Modified from Learmonth.)

a lower volume than usual, if fluid is introduced rapidly. This finding indicates that intravesical pressure rather than intravesical volume initiates the reflex. Roentgenograms show that until the reflex occurs, fluid is held at the junction of the bladder and the posterior urethra. The responses of the human bladder are identical.[6]

The results of action current studies demonstrate that the afferent impulses, responsible for the detrusor reflex, arise from stretch receptors in the bladder

wall and enter the spinal cord by way of the pelvic nerves.[13] The tonic state of moderate contraction characteristic of the cat's bladder is associated with a constant outflow of pelvic impulses to the fundus and the bladder neck.[7] It is only when the bladder is greatly distended that action potentials appear in the afferent fibers of the hypogastric nerves.[13] Tonic contraction of the external sphincter is maintained by efferent impulses which pass along the pudic nerves. Bladder filling produces a sudden increase in the number of action potentials per unit time which reach the fundus and the bladder neck. When the intravesical pressure reaches a certain value, the detrusor muscle contracts (Barrington's first reflex) and the posterior third of the urethra relaxes (the sixth reflex). At the same time, the sudden absence of efferent discharges over the pudic nerves (central inhibition) results in the relaxation of the compressor urethrae muscle (the fifth reflex) and the bladder is effectively emptied.

TABLE CXXIV

THE BLADDER REFLEXES (FROM DATA PUBLISHED BY BARRINGTON[1-4])

REFLEX	EXCITING STIMULUS	AFFERENT ARM	EFFERENT ARM	RESPONSE	REFLEX CENTER
First	Distend bladder	Pelvic	Pelvic	Bladder contraction	Hind-brain
Second	Fluid through urethra	Pudic	Pelvic	Bladder contraction	Hind-brain
Third	Distend posterior urethra	Hypogastric	Hypogastric	Bladder contraction	Cord
Fourth	Fluid through urethra	Pudic	Pudic	Relax urethra	Cord
Fifth	Distend bladder	Pelvic	Pudic	Relax urethra	Cord
Sixth	Distend bladder	Pelvic	Pelvic	Relax posterior third of urethra	Cord

The act of micturition is facilitated by the passage of fluid through the urethra. This stimulus sets up impulses which enter the spinal cord over the pudic nerves[13] and reflexly produces contraction via the pelvic nerves (the second reflex) and relaxation of the urethra by way of the pudic nerves (the fourth reflex). Distention of the posterior urethra by high intravesical pressure is said to result in contraction of the detrusor muscle (third reflex). The afferent and efferent pathways are located in the hypogastric nerves. Doubt has been cast upon the existence of the third reflex, for in man dilatation of the posterior urethra produces no vesical contraction, nor is any sensation noted.[6] The bladder reflexes are of such a nature that vesical distention results in an orderly sequence of events.

Effects of Transection of the Spinal Cord.—If the bladder of a cat which has suffered transection of the spinal cord or medulla is distended by successive increments of fluid, the bladder contents are not suddenly and completely emptied.[1, 2] It is only when the intravesical pressure becomes sufficient to force open the urethra that fluid escapes, and then only in drops. As soon as the pressure falls below the threshold value, retention supervenes. One to two weeks after transection of the spinal cord the urethral resistance diminishes. When a large quantity of urine is present, its manual expression is facilitated if, after evacuating the bulk of it, the external pressure is removed for a few minutes. It is then found that the bladder which was previously lax has contracted and the remainder of the urine may be expressed easily. The reflex nature of this phenomenon is demonstrated by the fact that such a bladder contraction never occurs in cats which have lost the function of their sacral roots. The decrease in urethral resistance is associated with the escape of

urine from the urethra in rhythmic jets. While a series of such jets may amount to a considerable volume of urine, the fluid discharge always ceases before the bladder is emptied. If overdistention is allowed, hematuria occurs. It is of considerable interest to note that clinical reports of the state of the bladder following transverse cord sections in man closely parallel the descriptions of bladder activity in the spinal animal.[8]

The loss of bladder function shown by spinal animals must be related to the interruption of central pathways which extend high into the central nervous system. Barrington[2] has shown that the reflex arcs of the first and second reflexes are broken when the brain stem is sectioned at, or below, the mid-pontine region. Partial sections of the spinal cord at various levels indicate that centripetal and centrifugal paths lie in the dorsal half of the lateral columns near the periphery. Bilateral destruction of these small parts of the cord gives rise to the same disorganization of micturition as a complete spinal transection.[5] The reflex centers of the other four reflexes are located in the lower part of the spinal cord.

Effects of Lesions of the Peripheral Nerves: *The Pelvic Nerves.*—Bilateral division of the pelvic nerves in the cat results in urinary retention for several days.[1] In expressing urine from these bladders, it is necessary to maintain a constant steady pressure until the urethral resistance gives way. Even then, the bladder will not continue to empty if the pressure is decreased. It is impossible to empty the bladder completely in this way, for the laxity of the partially emptied viscus prevents the necessary pressure from being exerted upon the vesical contents. The giving way of urethral resistance is regarded as a reflex dilatation of the urethra (the fourth reflex). If the bladder is not emptied, it becomes overdistended and urine dribbles away. In time, the bladder distention leads to submucous hemorrhage, ulceration, and hematuria. Even in this condition the animal shows no signs of discomfort or bladder tenderness, suggesting that the pain of retention travels over the pelvic nerves. Two to twenty-nine days after operation, such cats deliberately select places for urination and squat to perform the act in the usual manner. The stream of urine is always feeble and only small quantities are voided. Although several acts of micturition may occur, posturinary palpation of the abdomen indicates that a considerable degree of retention is present. The bladder muscle of these animals shows considerable hypertrophy.[9]

The Pudic Nerves.—If the pudic nerves are cut in animals which have previously undergone pelvic nerve resection, urine drips away while the cat is walking about. When the bladder is squeezed, little or no urethral resistance is encountered. Voluntary acts of squatting to urinate no longer occur. It is evident that the integrity of the pudic nerves is necessary for the maintenance or for the inhibition of urethral tone as well as for the sensation which makes a cat with divided pelvic nerves conscious of the fact that it is about to pass urine. There are certain reasons for believing that in normal cats the impulses concerned with the desire to micturate are carried by the pelvic nerves.

Section of the pudic nerves in a normal cat results in a paralysis of the external sphincter which may lead to a slight degree of incontinence.[3] Similar injury in man is without any notable effect upon micturition.[10]

Division of the Sacral Posterior Roots.—In cats this produces symptoms quite analogous to those observed in patients with tabes dorsalis.[9] The operation

is constantly followed by a relaxed condition of the bladder which is more marked than that present after section of both pelvic nerves or after transection of the spinal cord.[1] Retention of urine is always present, and unless this is relieved, urine escapes in drops, but never in jets. Roentgenograms show that urine is constantly present in the posterior urethra. The "dead, persistent, powerful resistance" and the laxity of the bladder render complete emptying impossible. No improvement takes place during the subsequent life of the animal.

The Hypogastric Nerves.—In cats, section of the hypogastric nerves is followed by increased frequency of urination.[1] A transient frequency may be present after sympathetic nerve resection in man.[10] In neither species is the sympathetic innervation essential for micturition.

Bladder Sensations in Man.—The sensations of bladder filling, of painful distention, and the conscious perception of the desire to micturate are related to afferent impulses which are carried in the pelvic nerves.[10] And yet, the report that all of these sensations were experienced by a patient who had suffered complete lesions of the lower four sacral posterior roots indicates the sensory importance of the sympathetic pathway.[12] Further investigation has shown that, in man, the mechanical stimulation of the central end of a cut hypogastric nerve results in pain unless the spinal anesthesia extends above the ninth thoracic segment. In certain patients, vesical pain is said to be relieved by presacral nerve section.[10] A consideration of the sensory innervation of the bladder suggests that this operation must be expected to fail in many cases.[9]

The Cerebral Control of the Bladder.—Personal experience demonstrates that when the ordinary adult feels the urge to micturate, he can restrain the act until the proper opportunity for emptying the bladder presents itself. Voluntary restraint consists of the inhibition of vesical contractions, the closure of the external sphincter, and the contraction of the perineal muscles.[6] The internal sphincter, which is not under voluntary control, contracts and relaxes in reciprocal relationship with the detrusor muscle. When the intravesical pressure is sufficiently great, the "lifting" of voluntary restraint can evoke powerful contractions of the bladder. These may lead to reflex relaxation of the sphincters and bladder evacuation. While the external sphincter can be closed at will, its opening is reflexly produced by vesical contraction.[6]

It is generally conceded that the absence of inhibitory control shown by the infant bladder is related to the lack of cortical development. This conception is supported by the observation that certain lesions of the suprasegmental parts of the central nervous system produce a bladder which is functionally identical with that of the baby.

Experimental studies indicate that the cerebral cortex of animals exerts some control over bladder function. In the normal cat, the quantity of urine passed at each act varies greatly. Following cortical extirpation, the volume of fluid passed at each micturition becomes much more constant.[14] This observation suggests that the cerebral cortex modifies the reflex threshold concerned with the act of micturition.

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Part IV

The Respiration

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Part V

Metabolism and Nutrition

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Parts VIII and IX

Water Balance and the Kidney

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